

Chapter 2

Microbes, Metabolites and Health

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1 Introduction

High throughput DNA sequencing has revolutionised the analysis of complex communities of microorganisms (microbiota). In humans, this paradigm shift, allowing analysis of the membership of microbial communities without the need to culture individual organisms, has spawned an avalanche of research and a number of important collaborative programs characterising not only the catalogue of species comprising the microbiota associated with different ecological niches in the body in states of both health and disease (Group et al. 2009) but also their genetic potential (Qin et al. 2010). Nowhere in the human body are the microbes more numerous or the microbiota more complex than in the colon of the gastrointestinal tract (Savage 1977). With its trillions of bacteria, comprising over one thousand individual microbial species present in varying abundances, the microbiota of the human gut and the genes they carry (collectively the microbiome) provides the host with a vast metabolic potential over and above that afforded by the 20,000–25,000 protein coding genes of the human genome.

The composition of the human colonic microbiota is remarkably diverse between individuals with each person's microbiota being unique (Qin et al. 2010; Yatsunenکو et al. 2012). Despite this diversity at the taxonomic level, when analysed for functional potential by whole genome analysis at the gene level, conservation of bacterial genes between individuals was high suggesting that

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diverse microbial populations could deliver very similar functional outcomes for both the microbial community and the host (Huttenhower et al. 2012).

There is growing evidence that the gut microbiota impacts significantly on the health of the host. Animal studies have shown that the gut microbiota plays a key role in the post-natal maturation of both the gut itself and the gut immune system (Smith et al. 2007; Chung et al. 2012). In humans, changes in gut microbiota structure have been associated with gut-associated disorders including: inflammatory bowel diseases (Gevers et al. 2014; Frank et al. 2007; De Cruz et al. 2015) and colorectal cancer (Garrett 2015); metabolism-related disorders such as obesity (Ley et al. 2006), metabolic syndrome (Le Chatelier et al. 2013; Haro et al. 2016) and diabetes (Qin et al. 2012) but also with systemic disorders including cardiovascular disease, neurodegenerative diseases including Alzheimer's (Alam et al. 2014; Naseer et al. 2014) and Parkinson's (Goldman et al. 2014; Scheperjans et al. 2015) diseases and neuro-developmental and psychiatric conditions including autism spectrum disorder (Louis 2012; Mulle et al. 2013) and schizophrenia (Nemani et al. 2015).

Of these disorders, the role of the microbiota has probably been studied most extensively in obesity which is also a well-recognized risk factor for many of the other chronic diseases mentioned above. Obese humans, when compared to normal weight individuals, displayed a reduced ratio of microbes from the *Bacteroidetes* phylum relative to those of the *Firmicutes* phylum in their faeces and this ratio increased in obese individuals who lost weight (Ley et al. 2006). Important insights into the functional significance of these associations have come from the use germ free, gnotobiotic and gene mutant animal models. This same relationship of *Bacteroidetes* to *Firmicutes* was also observed in obese mice carrying two copies of the *ob* mutation in the leptin gene (*ob/ob* mice) relative to their *ob/+* and *+/+* litter mates. In this animal model, biochemical analyses revealed that these different microbiota varied in the efficiency of energy harvest from the diet and that both the obese-prone and lean phenotypes was transferrable to germ free mice by colonization with the microbiota from obese and lean donors respectively (Turnbaugh et al. 2006). This same result was observed when human faecal microbiota from female twins discordant for obesity were used to colonize germ free mice (Ridaura et al. 2013). Mice practise coprophagy. Co-housing of mice, conventionalised with the obese twin's microbiota, with other mice conventionalised with the lean twin's microbiota prevented acquisition of the obese phenotype. Microbial community analysis revealed that this prevention of obesity was associated with an invasion of *Bacteroidetes* from the lean microbiota into the microbiota of the obese-conventionalised animals (Ridaura et al. 2013). Interestingly this effect was diet-dependent and was most marked when the animals were fed a diet high in fruit and vegetables. When the animals were fed a diet high in saturated fat and low in fruit and vegetables, levels of *Bacteroidetes* invasion from the lean conventionalised animals was very low (Ridaura et al. 2013) highlighting the importance of diet as a selective force in gut microbiota structure/function determination. While microbial population changes associated with diseases have been extensively studied, the mechanisms by which these changes elicit their physiological effects on the host are just beginning to be unraveled.

Metabolites and other products made by the gut microbiota play a key role in the dialogue between the gut microbiota and the host. Contributions of the gut microbiota to the nutritional wellbeing of the host are well known and include the provision of vitamin K, B group vitamins, B12, biotin, riboflavin, thiamine and folate (Koenig et al. 2011; Said 2011) and amino acids (Yatsunenkov et al. 2012). However, gut microbes also make a vast array of proteins, peptides and low molecular weight metabolites and chemically transform others of host or bacterial origin, all of which impact on the structure and functionality of the microbiota and the health of the host (Nicholson et al. 2012). Some bacteria help shape their local community by producing bacteriophage or bacteriocins to kill off specific competitors. The production of bacteriocins by commensal *Escherichia coli* can, for example, inhibit the invasion of their niche by pathogenic *E. coli* O157:H7 (Schamberger and Diez-Gonzalez 2002). Others form feeding chains where one species performs an initial break down of a starting nutrient source to release intermediate breakdown products that can themselves provide substrates for other types of bacteria as exemplified using in vitro fermentation studies to examine the degradation of dietary glycans (Leitch et al. 2007a, b) and host-derived mucins (Png et al. 2010). Others can induce the host to create local environments that provide a colonisation and proliferation advantage for themselves and potentially other bacteria (Collier et al. 2008), while others can have direct effects on host functions e.g. the production of gamma amino butyric acid (GABA) (Barrett et al. 2012), the major inhibitory neuro transmitter in the mammalian central nervous system (CNS) with a major role in the regulation of muscle tone in humans. Although GABA produced peripherally does not cross the blood brain barrier and hence is unlikely to impact on CNS functions, it may modify gut motility and blood pressure (Inoue et al. 2003).

Likewise the host helps shape the gut microbiota through the secretion of bioactive molecules into the lumen of the gut. Defensins, (Gallo and Hooper 2012) secreted from the Paneth cells and most enterocytes of the gut mucosa, and IgA (Cerutti 2008), secreted from plasma cells in the lamina propria and through the gut epithelium, provide protection against overgrowth of many pathogenic microbial species. Further, using a germ free/gnotobiotic maternal separation mouse model of stress it has been demonstrated recently that stress can alter the colonic environment leading to an altered colonic microbiota. While this altered microbiota was insufficient to recapitulate the stress-associated changes in host physiology upon microbial transplantation to non-stressed germ free animals, transplantation was associated with a transfer of anxiety-like behavior and behavioral despair but the molecular effectors are yet to be defined.

So what are the key influencers of gut microbiota structure and function and how might they elicit their impacts on health? While the gut of the near term foetus may have some microbes present, the numbers are very low (Jimenez et al. 2008). The mode of delivery (vaginal vs. caesarean section) impacts significantly on the structure of the gut microbiota of the neonate (Dominguez-Bello et al. 2010) with vaginally delivered infants developing bacterial communities resembling those of their mother's vaginal microbiota, while the gut microbiota of caesarean-delivered infants' reflected more closely those of their mother's skin. Prior to weaning the gut

microbiota is relatively simple, dominated by Bifidobacteria and lactic acid bacteria. This changes significantly with the introduction of solid food, acquiring something close to its mature composition by the time of their first birthday (Backhed et al. 2015; Favier et al. 2002; Koenig et al. 2011). The base microbial population structure of a human's colon is relatively stable through childhood and much of adult life but begins undergoing change and simplification with aging and associated changes in health status, diet and lifestyle (Claesson et al. 2012). Despite this stability of an individual's core microbiota, components still show a dynamic response, both in composition and biological functionality, to changing dietary and environmental conditions (Clemente et al. 2012). Diet composition, in particular the amounts and nature of non-digestible components of the diet, can modify the of gut microbiota markedly (Gibson and Roberfroid 1995; Flint et al. 2012). Dietary fibre is the best understood of these. Epidemiological studies have associated diets high in dietary fibre with a reduced risk of a number of disorders including colorectal cancer and inflammatory bowel diseases (Hou et al. 2011). Here we discuss what is known about dietary fibre, the early research implicating it in promotion of gastrointestinal health, its interaction with the gut microbiota to produce a range of bioactive metabolites and our growing understanding of how these metabolites elicit their associated health benefits in the host.

2 Dietary Fibre and Gut Health: A Brief History

The high community awareness of the health potential of dietary fibre is relatively new. This interest was triggered by early work of a number of British physicians in South and East Africa. They saw that native Africans ate a diet high in whole grain foods and were essentially free of the non-infectious diseases which affected Europeans living in the same geographical area who ate highly refined foods (Burkitt 1973). Initially, they focused on large bowel disorders including constipation, diverticular disease, appendicitis and related problems. They linked these differences to their dietary fibre intakes and suggested that the disease profile of the Europeans reflected a simple dietary fibre deficiency. These early studies relied on observation (not measurement) and were quite limited in scope. They were limited also by the early definition of dietary fibre as plant cell wall material resistant to human small intestinal enzymes i.e. indigestible and largely insoluble plant material. The total indigestibility of these non-starch polysaccharides (NSP) explained their faecal bulking and laxating effects and protection against large bowel diseases very neatly (Cummings et al. 1992). However, fibre (as NSP) has proved very disappointing for protecting against other diseases of affluence, especially colorectal cancer (CRC), where it was expected to lower risk substantially. While some studies (e.g. the European Prospective Investigation into Cancer and Nutrition, EPIC) have shown a dose-dependent reduction in CRC risk (Murphy et al. 2012), others have not (Park et al. 2005; Lanza et al. 2007). The Australian paradox also fits with these inconsistencies. Australia seems to be one of the few countries where

fibre consumption has increased substantially over time with a reported population average of 28 g/person/day (Baghurst et al. 1996) but CRC morbidity and mortality rates remain high (AIHW 2012). This paradox is leading to a revision of the relative importance of the different components which contribute to fibre intake in low risk populations and also the way in which dietary fibre actually works in the large bowel.

Much of the credit for the popularization of the dietary fibre hypothesis is due to Dennis Burkitt (Trowell and Burkitt 1987) but it seems that the focus on fibre as an indigestible bulking agent may be misplaced. It is now impossible to quantify actual food consumption rates in the original African population. Changes due to urbanization and higher incomes have altered the traditional rural lifestyle patterns of native South Africans so that their activity levels and total dietary fibre (TDF) consumption have fallen. TDF intakes have declined from an estimated 25–35 g/person/day (2 generations ago) to 15–20 g/person/day (now) (Segal et al. 2000). One would have expected this to lead to an increase in CRC rates but this does not seem to have happened. Comparison of the diet of indigenous Africans in South Africa and African Americans in the United States shows that they are quite similar in their low TDF content (O’Keefe et al. 2007) but the latter have one of the highest global rates of CRC of any ethnic group. One suggestion is that the high content of animal products in the African American diet is responsible. It is true that CRC risk has been linked to greater consumption of red and processed meat (Norat et al. 2005) but the work of Walker and others suggest very strongly that the type of fibre consumed by Africans may be equally important (Walker et al. 1986). The original concept underpinning the differential in disease risks was the high whole grain consumption of the Africans. Put simply, the notion of “fibre” came later, essentially as roughage (Topping and Illman 1986). However, it has emerged that the culinary habits of the Africans are an important factor. Many native South Africans consume reheated or cold maize porridge on a daily basis, particularly in rural areas. Cooking gelatinises the starch, increasing its small intestinal digestibility but cooling leads to self-association of the chains. This process (retrogradation) leads to resistance to amylolysis i.e., the formation of resistant starch (RS). Resistance to amylase is a key feature of TDF meaning that RS is also a fibre component. It has been shown that hot traditionally cooked maize meal contains 18 g of RS/100 g while cooked and cooled maize contains a higher RS content than that of a hot maize meal (Heneker et al. 1998). Cooking is not the only factor. The amylose content of South African maize is 37–40 % of total starch which is relatively high (37.1–39.9 %) (van der Merwe et al. 2001). Amylose is a relatively compact starch polymer which is slower to gelatinize than amylopectin and also quicker to retrograde meaning that it is digested more slowly than low amylose starches and also yields more RS in food products.

One of the most important observations driving the reappraisal of the relative importance of fibre (i.e., NSP and RS) was the lack of relationship between TDF and bowel habit in native South African children. This has led to the current focus on the role of the microbiota in human health, specifically through the production of short chain fatty acids (SCFA). Knowledge of the existence of RS is not new nor is

the presence of SCFA in the large bowel of omnivores (Elsden et al. 1946). It was known that TDF polysaccharides are lost during whole of gut transit (Schneeman 1986). For NSP, the extent of loss varies by source and ranges from ~ 0 (for cellulose) to $>90\%$ for pectin. In contrast very little starch appears in normal human faeces which, coupled with its susceptibility to amylolysis, gave the obvious conclusion that small intestinal starch digestion was complete. The existence of potentially significant levels of indigestible starch (i.e., amylase resistant starch—RS) in foods was shown by Englyst and colleagues (Englyst et al. 1982). There was earlier (indirect) evidence from Levitt's laboratory (Anderson et al. 1981) in intact humans showing that, following consumption of a low-fibre convenience cereal product, breath H_2 evolution rose significantly. Breath H_2 is a marker for large bowel fermentation and their observations can now be interpreted as showing the presence of RS and also that fermentation was occurring. Both are now established as significant factors in human gut physiology (Topping and Clifton 2001). RS is defined in terms of starch which escapes into the large bowel and the products of its fermentation. RS is today recognized as a component of fibre and not a separate entity.

There are striking similarities between large bowel fermentation by the microbiota of humans and other omnivores and that of obligate herbivores (Topping and Clifton 2001). The end products are similar i.e., SCFA (principally acetate, propionate and butyrate), gases (CH_4 , H_2 and CO_2) and the energy to fuel bacterial growth. In humans and relevant model species (most notably pigs), SCFA levels are highest in the proximal large bowel and decline with passage of the digesta stream. This is consistent with the high production rates in the caecum and proximal colon i.e., where substrate availability is greatest. The fall in SCFA levels along the colon reflects substrate depletion but also their uptake by the large bowel so that $<10\%$ of total production is excreted in faeces. This distributional profile has very important implications for gut health and is believed to relate to the higher prevalence of non-infectious disease in the distal colon and rectum (Topping and Clifton 2001; Cats et al. 1996).

SCFA have a number of general effects which contribute to large bowel health (Topping and Clifton 2001; Brouns et al. 2002; Wong et al. 2006). Their production acidifies the digesta which inhibits the overgrowth of potential pathogens and limits the absorption of potentially toxic compounds e.g. NH_3 . The latter cannot enter colonocytes as NH_4^+ so lower pH values limit their exposure to this and other cytotoxic and genotoxic agents (Topping 2007). A study in normal humans consuming their usual diets with supplements of NSP or NSP + RS showed an increase in faecal NH_3 excretion which correlated closely with greater butyrate excretion (McOrist et al. 2011). This is consistent with diminished absorption by (and less exposure to) colonocytes. SCFA enhance visceral blood flow through dilation of resistance vessels in the colon which facilitates O_2 supply (Topping and Clifton 2001). The history of research in dietary fibre is littered with misconceptions, revisions and reappraisals. The current focus on the microbiome is another case in point. The emergence of modern technologies has given us an opportunity to identify the species which are present and how they are altered by diet. Previously,

this was almost impossible using the techniques of traditional microbiology. However, it should be noted that it is the products of bacterial action in the large bowel which influence human health. While they have these general effects, the individual acids have specific actions which benefit visceral function, health and wellbeing.

3 Dietary Fibre: a Complex Mixture

Dietary fibre is not a single entity but an umbrella term for a large, diverse group of substances, predominately but not exclusively carbohydrate polymers of plant origin, that pass through the small intestine and undergo partial or complete fermentation in the colon.

The global consensus definition of dietary fibre (Codex 2010), has broadened from a botanical and structural focus (plant cell wall polymers) and now captures other salient properties of fibre, notably compositional diversity and physiological functionality.

The major classes of dietary fibre are NSP, RS and non-digestible oligosaccharides although inclusion of the latter can vary with jurisdiction (Codex 2010). Fibre also includes analogous compounds, non-digestible carbohydrate polymers, of animal origin, and plant secondary metabolites that are intimately associated with plant cell wall polysaccharides, notably lignin.

Fibres, both natural and synthetic, differ markedly in their physiological properties and capacity to promote human health (Dahl and Stewart 2015; Bird 2007; Cummings and Stephen 2007; Buttriss and Stokes 2008; Brownlee 2014; Edwards et al. 2015). While physiological functionality is included in the definition of fibre, it is applied only to foods containing carbohydrate polymers sourced from either raw food materials or chemically synthesized. A demonstrable beneficial physiological effect in humans is a requirement for foods to be advertised as containing added/functional fibre.

A prerequisite property and defining feature of fibre is that it is potentially fermentable by colonic microbiota. In recent times there has been growing scientific and commercial interest in highly fermentable fibres, notably non-digestible oligosaccharides and resistant starches, owing to their favourable effects on gut microbiota composition and activity, and host health (Bird 2007; Conlon and Bird 2015; Bird and Topping 2001; Broekaert et al. 2011, de Menezes et al. 2013).

NSP, mainly cellulose and hemicelluloses, and lignin, are the fundamental structural elements of plant cell walls and have been integral to all descriptions of dietary fibre (Miller Jones 2014). Cellulose and hemicelluloses are widely distributed in the plant kingdom and are ubiquitous in the plant foods that humans eat. NSP typically comprise long chains of monosaccharides, mostly glucose moieties, joined by β -1,4 linkages. Cellulose is a high molecular weight homopolymer consisting of linear β -1,4 linked-chain of glucose units. The chains are closely packed and the hydrogen bonds that form between adjacent chains ensure that this

structure is highly resistant to digestion by human hydrolases, which specifically attack monosaccharide units linked by α -1,4 and α -1,6 bonds (Tunland and Meyer 2002; Englyst et al. 2013). Hemicelluloses, in contrast, are smaller, branched, heteropolymers comprising a variety of monomeric units, commonly xylose and arabinose, and mannose, glucose, rhamnose and glucuronic acid, joined by various types of chemical bonds. Hemicelluloses comprise a large variety of glycans, both water insoluble and soluble (Tunland and Meyer 2002; Englyst et al. 2013).

NSP generally conform to the notion of “insoluble fibre” and are concentrated in highly fibrous foods such as cereal brans (Bird 2007). Fibres such as β -glucans and arabinoxylans tend to be water soluble (water extractable). Other examples of soluble non-starch polysaccharides include gum arabic (acacia gum), guar gum, psyllium, pectins and alginates (Tunland and Meyer 2002; Englyst et al. 2013). However, solubility is not strictly a fixed property. Mixed-linkage glucans, such as those found in oats and barley, exhibit varying degrees of solubility depending on the source, analytical methodology and grain processing (Tosh et al. 2008; Agbenorhevi et al. 2011).

RSs are starches which escape small intestinal digestion. Like highly digestible starches, RS is a polymer of glucose monomers joined α -1,4 and α -1,6 glycosidic linkages at branch points and hence are not intrinsically resistant to digestion by enteric enzymes of humans. Rather they are rendered less accessible to the amylases of the upper gastrointestinal tract by some feature of the starch itself, e.g. its physicochemical state and/or the physical complexity of the food matrix in which the starch is presented e.g. whole grains or some feature of the host e.g. compromised dentition or a rapid food transit through the upper GI tract (mouth, stomach, small intestine) (Bird et al. 2000). In particular, the duration of exposure of ingested starch to hydrolytic processes in the upper gut, which is governed by gut motility and digesta transit rate, is a major determinant of the amount of dietary starch reaching the colonic microbiota. RS therefore represents the sum of the undigested starch and intermediates of starch digestion that are not absorbed in the small intestine and hence enter the large bowel of healthy humans (Bird et al. 2010, 2012). While most fibres are reasonably stable to culinary practices, RS can be formed or easily depleted by cooking and other processes involved in food production and preparation (Bird et al. 2012).

Non-digestible oligosaccharides are important contributors to the total fibre content of many plant foods. They are low molecular weight fibres that have a degree of polymerization (chain length; DP) between 3 and 9 (de Menezes et al. 2013; Englyst et al. 2013). Fructans are polyfructoses consisting of 3–20 units with a terminal glucose unit (Gibson et al. 2004; Roberfroid 2005). Food sources rich in fructans include Jerusalem artichoke, onions, garlic and bananas. Legumes, such as soybeans, contain galactooligosaccharides (raffinose, stachyose and verbascose) (Muir et al. 2009). Cereal fructans consist of straight and branched chain fructose polymers (Jenkins et al. 2011). Commercial sources of dietary fructans, commonly derived from chicory, inulin and fructooligosaccharides (FOS), are extensively used as food ingredients (Roberfroid 2007). Inulin is a large molecule with a DP of

between 2 and 60 fructose residues whereas FOS comprises smaller molecules with a DP between 2 and 8. 'Oligofructose' is a partial enzymatic hydrolysate of inulin.

Fibre also encompasses a range of other plant substances, including lignin, cutin, waxes, suberin, tannins, saponins and phytosterols, that are naturally associated with botanical cellular structures (Bird 2007; Englyst et al. 2007; Miller Jones 2014). Lignin is a heterogenous polyphenolic ether, not a carbohydrate, that is covalently bonded to cellulose (Tunland and Meyer 2002). Most of these substances are quantitatively minor constituents of human diets and are not metabolized extensively by the gut microbiota (Topping and Clifton 2001). However, they may impair fermentation of plant structural and storage polysaccharides (Stephen 1994; Edwards et al. 2012).

In certain disease settings, dietary carbohydrates that are normally digestible in the upper gut ('available carbohydrate') can also make their way to the colon and essentially function as dietary fibre. For instance, lactose can be an important substrate for the microbiota in those individuals with lactase deficiency (Deng et al. 2015; Lukito et al. 2015; Wahlqvist 2015; Windey et al. 2015). The contribution of this carbohydrate is dependent on the degree of lactase deficiency. Other bowel diseases and conditions that compromise the functional capacity of the upper gut, such as celiac and Crohn's diseases, will also increase the amount of malabsorbed carbohydrate, and other dietary constituents, reaching the colonic microbiota (Conlon and Bird 2015).

Physicochemical and functional properties of fibre, including solubility in water, viscosity and gel formation, and water holding capacity, have formed the basis of various classification schemes. Soluble/insoluble fibre classification has proven popular, however it is inconsistent with the accepted definitions for fibre and is an unreliable predictor of physiological function. 'Solubility' relates to an *in vitro* environment, not the gut lumen. The proportion of fibre that is solubilised is often a function of the assay conditions used and in many instances the results are method specific (Cummings and Stephen 2007; Englyst et al. 2007). The proportion of soluble fibre can also change during food processing and passage of the fibre through the upper gut (Arrighi 2001; Comino et al. 2016).

Dietary fibres can be classified on their fermentability (Dahl and Stewart 2015; Slavin 2001). But, gauging the rate and extent of fibre fermentation *in vivo* is challenging, which is why knowledge of fermentation of fibre-rich substrates is based largely on studies deploying *in vitro* techniques. These commonly use human faecal inocula in static and flow-through incubation systems to simulate conditions and events in the complex, anaerobic and highly dynamic micro-ecosystem of the large bowel. As such, they provide limited indicative data on fibre degradation by the colonic microbiota.

Generally, about 70 % of the fibre that is consumed by people on mixed diets is considered to be fermented to completion in the colon (Slavin 2001; Topping and Clifton 2001). However, individual fibres vary markedly in their fermentability although most are partially fermentable. Water soluble fibres, such as those from vegetables & fruits, are usually more easily fermented compared to insoluble fibres, such as cellulose, which is quite resistant to fermentation. For instance, only about

30 % of the fibre contained in wheat bran is fermented completely in humans (Topping and Clifton 2001). Not surprisingly, degradation of the smaller molecular weight carbohydrates and soluble NSPs occurs in the more proximal regions, whereas the breakdown of fibre that is more difficult to ferment occurs further along the large bowel. In general, the colonic microbiota metabolises individual fibres in the following order: mono- and oligosaccharides are preferentially fermented followed by starches, soluble NSPs (soluble β -glucans, arabinoxylans) and then insoluble NSPs (Bach Knudsen 2015). However, there are many exceptions to the rule.

There are myriad factors that influence the rate and extent of fermentability of carbohydrates aside from the colonic microbiota per se. Physicochemical attributes are the primary intrinsic determinants, notably chemical structure (monosaccharide composition, linkage type) and molecular size (chain length) but diet, food form (matrix and particle size) and physiological factors that alter the gut microbial habitat, such as digestive and absorptive capacity and digesta transit time, are also important, as is the amount (dose/concentration) and composition of fibre-containing foods in the diet.

The fibre content of most western diets is exceedingly low and consequently, so too are fibre intakes. Many populations consume inadequate amounts of fibre, falling well short of intake targets recommended by health authorities (i.e., ~ 14 g total fibre/1000 kcal or ~ 30 g dietary fibre/day for an adult) (Dahl and Stewart 2015; Baghurst et al. 1996). Furthermore, there is a limited diversity of fibre components in most modern diets. Insoluble NSP predominate (Baghurst et al. 1996; Conlon and Bird 2015). Oligosaccharides are consumed in much smaller amounts, whereas resistant starch is essentially nonexistent in most modern diets simply because modern processed and staple foods contain only small amounts (Bird et al. 2012).

Ancestral hunter-gatherer diets provided five times more fibre than do contemporary diets (Eaton 2006, Leach 2007). The range of fibre sources would also have been considerably greater than that consumed by modern populations, which suggests that our early forebears harboured a much larger, richer and more diverse gut microbiota.

Cereals and cereal products are the major source of fibre for most human populations, but the variety of cereal sources is limited (Baghurst et al. 1996). Wheat predominates and its increasing worldwide popularity explains why insoluble NSP such as cellulose and arabinoxylans, are the major type of dietary fibre for most people. Fruits and vegetables are the next most important source of fibre but they too tend to supply mainly NSP (Baghurst et al. 1996). There is also an increasing range of synthetic fibres (e.g. chemically modified resistant starches such as cross-bonded starches) in processed foods. Most are derivatives of plant polymers.

NSP account for the major portion of dry matter (20–45 %; equivalent to 10–25 g/day) supplied to the colon of individuals consuming western diets (Conlon and Bird 2015). Monosaccharides and oligosaccharides account for a further 10 %, and RS, which includes partial hydrolysis products, is unlikely to be more than 10 % (Conlon and Bird 2015); Small quantities of sugar alcohols also serve as

fermentable substrates but the amount and type is very much diet dependent (Grembecka 2015; Halmos et al. 2015; Muir et al. 2009; Tennant 2014).

Interactions between different fibre components in a food as well as its physical form (matrix), in particular the structural integrity of plant cell walls, will influence the rate and extent of fermentation of the component fibres. Milling, processing, preparation and storage conditions of foods can alter their fibre content and functionality and hence their impact on the gut microbiota (Tuohy et al. 2012). For instance, soluble fibre may be lost through leaching during the cooking process. Heat treatment may solubilise certain fibres, thereby increasing the ratio of soluble to insoluble fibre. Short chain fructans can be degraded by yeast enzymes and also exposure to acidic conditions. A sufficiently large particle size is needed to ensure an intact cell wall structure resists extensive fermentation. Coarse bran loses both its water holding capacity and some of its laxative effects when it is finely ground simply because it is more extensively fermented in the large bowel (Topping and Bird 1999).

Another important consideration is functional capacity of the upper gut. Small intestinal digesta transit rate and nutrient assimilation can differ markedly among people. For instance, some individuals are especially efficient in digesting and fermenting starch (Thornton et al. 1987). Furthermore, some fibres may undergo degradation in the upper digestive tract owing to the action of bacterial glycanases in that region of the gut (Bach Knudsen 2015). However, the loss of fermentable substrate is probably small.

Poorly fermented carbohydrates may alter the metabolic capacity of the gut microbiota through various mechanisms. For instance, by acting as a physical scaffold for colonic microbes, resident and transitory, it may facilitate the fermentation process. Fibres in general also influence fermentation events by augmenting intestinal motility and flow of the faecal stream (Topping and Bird 1999; James et al. 2015).

4 Dietary Fibre and Its Interaction with the Gut Microbiota

The dietary fibres described in the previous section have distinct effects on the gut microbiome. This can be because of their solubility, structure or where in the gut the fibre is fermented. This differential effect will lead to selection of certain groups of bacteria, specific fermentation outputs, like SCFA and gas production, and likely inhibition of pathogenic bacteria.

Some of the most widely studied prebiotic fibres are inulin, fructooligosaccharides (FOS) and galactooligosaccharides (GOS) with the latter two encompassing numerous different types of fibres. All of these fibres are soluble and highly fermentable which means they are fermented in the terminal ileum or the proximal colon (Eswaran et al. 2013). FOS and GOS were both found to have a bifidogenic

effect and increased levels of *Lactobacillus* in both animals and humans (Davis et al. 2011; Djouzi and Andrieux 1997; Kleessen et al. 2007a). These effects were accompanied with higher levels of SCFA and a lower pH in the large bowel, however FOS were found to favour an increase in butyrate whereas GOS advocated for higher propionate levels (Djouzi and Andrieux 1997). FOS and GOS also had differential effects on gas production in rats, with FOS feeding increasing both hydrogen and methane excretion, but GOS only induced higher methane excretions (Djouzi and Andrieux 1997). Inulin seems to have differential effects in animals and humans. This difference was found albeit using a human microbiota-associated rat model. In the rat model, no difference in *Bifidobacterium* spp. was observed after inulin intake, but higher levels of fibre degrading bacteria *Roseburia* spp. and *Eubacterium rectale* were observed and a reduction in potentially pathogenic bacteria (*Clostridium* spp.) (Kleessen et al. 2007a; Van den Abbeele et al. 2011). SCFA concentrations increased and pH levels reduced with inulin intake in animals. Human intervention trials have not been able to replicate these changes. In these studies, higher levels of *Bifidobacterium*, *Faecalibacterium prausnitzii*, reduced numbers of *Bacteroides-Prevotella* and potentially pathogenic bacteria were observed (Kleessen et al. 2007b; Ramirez-Farias et al. 2009; Costabile et al. 2010). In a later study, Ramirez-Farias et al. (2009) showed that it was certain species of *Bifidobacterium*; *B. adolescentis*, *B. longum* and *B. bifidum* that changed with inulin intake. Another significant difference between the animals and human studies was the absence of changes observed in faecal SCFA levels in humans given inulin (Kleessen et al. 2007b; Costabile et al. 2010). Another way to evaluate the effect of certain fibres is to remove them from the diet. This was done by Halmos et al. (2015) in a randomised control crossover trial of a low Fermentable Oligo- Di- and Monosaccharides And Polyols (FODMAP) diet (no inulin) and a diet containing a typical level of FODMAP's found in an Australian diet. This study showed that by avoiding FODMAP the overall bacterial abundance, and the relative abundance of *Clostridium* cluster XIVa (butyrate-producing bacteria) and the mucus-associated bacterium *Akkermansia muciniphila* was reduced. However, these changes did not result in differences in faecal SCFA levels, although pH was higher on the low FODMAP diet.

A possible reason for not noticing any differences in faecal SCFA levels may well be because >95 % of the SCFAs produced in the human colon are taken up by the gut epithelia (Kleessen et al. 2007b; Costabile et al. 2010). This does not exclude that there might be a difference in SCFA levels in the proximal colon however, when SCFAs are measured in faeces, levels are diminished due to uptake along the colon.

RS, can also change the gut microbiome and the metabolic components produced, however the RS type plays an important role. All of the RS types are generally digested in the proximal and the transverse colon, but some are digested throughout the colon like RS type 1 and 4 (Clarke et al. 2011b; Eswaran et al. 2013).

Animal studies have revealed great benefit and potential for RS as a prebiotic fibre. A limited number of studies have been conducted using RS type 1; in animals

(rats), this type of RS did promote higher abundances of *Bifidobacterium* spp. and increased SCFA levels at month five compared to control (Kleessen et al. 1997). The RS type 2 fibre is often used in animal studies and seems to have a broader effect on the gut microbiota. It was shown in rat and pig studies that RS type 2 can increase the abundances of *Bifidobacterium* spp., *Lactobacillus* spp., *Enterobacteriaceae* and *Ruminococcus bromii* compared to control animals (Conlon et al. 2012; Abell et al. 2011; Kleessen et al. 1997; Le Blay et al. 1999; Martin et al. 1998). These microbial changes were accompanied by higher SCFA levels due to RS type 2 feeding with certain studies observing specific increases in propionate (Conlon et al. 2012; Abell et al. 2011) and butyrate (Conlon et al. 2012; Abell et al. 2011; Le Blay et al. 1999; Martin et al. 1998) excretion. RS type 3 have also been shown in rat and pig studies to select for *Bifidobacterium* spp., *Lactobacillus* spp. and *Faecalibacterium prausnitzii*, but lower the abundances of gamma-Proteobacteria (Conlon et al. 2012; Haenen et al. 2013). Again, these microbial changes were in conjunction with increased SCFA levels, especially butyrate and propionate. The gut microbiota can also be modified with RS type 4 with a rat study conducted with chemically modified RS showing increases in *Lactobacillus* spp. and *Parabacteroides distasonis* compared to control (Abell et al. 2011). This study also recorded increases in SCFA levels.

Human studies have confirmed many of the changes observed in the animal gut, however with a high inter-individual variation for both microbial and biochemical composition. Studies in humans are generally conducted using RS type 2, 3 and 4. RS type 2 and 3 have very similar effects in the human gut promoting higher levels of *R. bromii*, *F. prausnitzii* and *E. rectale* compared to a Non-Starch Polysaccharide (NSP) control (Abell et al. 2008; Martinez et al. 2010; Walker et al. 2011). For two of these studies, SCFA were also measured and the RS consumption was associated with higher levels of faecal SCFA levels, especially butyrate (Abell et al. 2008; Walker et al. 2011; McOrist et al. 2011). This increase in faecal butyrate levels successfully correlated with the increasing faecal abundance of *F. prausnitzii* and *E. rectale* (Abell et al. 2008; Walker et al. 2011). Human research studies have been conducted with RS type 4 showing beneficial effects on the gut microbiota with higher abundances of Actinobacteria, Bacteroidetes and a reduction in Firmicutes (Martinez et al. 2010), more specifically *Clostridium* cluster XIVa and IV, *Lactobacillus*, *B. adolescentis*, *P. distasonis* and *R. bromii* (Clarke et al. 2011b, Martinez et al. 2010; West et al. 2013; Le Leu et al. 2015). Reductions were also observed in bacteria, *Ruminococcus gnavis*, *R. torques* and *E. coli*, previously associated with gut diseases (Le Leu et al. 2015). RS type 4 consumption also resulted in higher SCFA level in the faeces of volunteers consuming these fibres. These substantial shifts in bacterial composition imply that the different RS types have the ability to select for certain groups of bacteria, despite a relative high inter-individual variation. Combined, these studies strongly suggest a key role for *R. bromii* in the degradation of RS and these bacteria have also been found to be the predominant ones to colonise RS (Leitch et al. 2007a; Ze et al. 2012). It is also worthwhile keeping in mind that these prebiotic effects are not universal, as some volunteers are non-responders. The response in any volunteer will always depend

on the initial composition of the gut microbiota which helps to explain the often large inter-individual variation seen in human intervention studies examining the gut microbiome.

Fibres, like NSP, with a very limited prebiotic effect because up to 75 % of the ingested fibre is not fermented in the gut (Backman 2009; Roberts et al. 2010) and no selective promotion of specific bacterial populations (Abell et al. 2008; Walker et al. 2011) can still affect the gut microbiota. It is suggested that NSP can interact with the intestinal bacteria via contrabiotic effects, whereby they prevent potentially harmful interactions between bacteria and the gut epithelium that occur upon dysbiosis (Backman 2009; Parsons et al. 2014; Roberts et al. 2010, 2013). The contrabiotic effect has been tested for a range of soluble NSP's and they are not all equally effective. NSP from plantain bananas and broccoli seems to have greater effect than NSP from apple and leek (Roberts et al. 2010). These tests have mainly been conducted in vitro testing the ability of the fibres to block the attachment of adherent, invasive *E. coli* (AIEC). Soluble plantain NSP's have not only been able to block AIEC but also adherent enteric pathogens, like *Shigella* spp., *Clostridium difficile*, enterotoxigenic *E. coli* and *Salmonella* spp. (Parsons et al. 2014; Roberts et al. 2013). Parsons et al. (2014) also demonstrated that NSP from plantain bananas can block Salmonellosis in chicken when added to their feed and translocation of *Salmonella* Typhimurium across isolated follicle-associated epithelium from human ileum. It is believed that microfold (M)-cells overlying Peyer's patches in the human ileum and lymphoid follicles in the colon are potential points of entry for AIEC (Roberts et al. 2010). It is suggested that the contrabiotic effect is mediated via an interaction between the soluble NSP and the epithelial cell causing an electrogenic chloride secretion preventing the adhesion of the pathogens (Parsons et al. 2014). Another and more simple explanation is the direct interaction between plantain NSP and *E. coli*, *C. difficile* and *Salmonellae* as they can all utilise plantain NSP as an energy source (Roberts et al. 2010, 2013).

5 Dietary Fibre, Short Chain Fatty Acids and Their Impact on Gut Health

Collectively, the microbes present within the GI tract can produce a vast array of bioactive compounds, many of which can influence the functions of host tissues. A comprehensive review of the many known gut microbe-derived metabolites and their functions can be found elsewhere (Nicholson et al. 2012). We will focus our discussion on the impacts of some of the primary fermentation end-products, particularly the SCFA, which are considered beneficial and largely a result of the breakdown of dietary polysaccharides, and some toxic products such as ammonia, phenols and hydrogen sulphide which are largely derived from fermentation of dietary protein.

The wide degree of variation in microbiota composition between individuals would be expected to be reflected in different gut microbial metabolite profiles and susceptibility to diseases. For example, levels of SCFA in the large bowel of humans vary by ten-fold, and although dietary and environmental factors contribute to the variation, microbial differences appear to play a major part (McOrist et al. 2011). Our understanding of what represents a normal or healthy complement of gut microbial taxonomic units is poor, as is our understanding of the factors which can disturb the commensal microbial populations and potentially impact health. Studies examining the cause(s) and potential treatments of inflammatory bowel disease (IBD) have provided our greatest insights into this area.

Gut microbes play a central role in the causation of IBD. For example, it is not possible to induce ulcerative colitis (UC) in germ-free animals (Sellon et al. 1998). Also, antibiotics can improve symptoms of IBD (Khan et al. 2011), as can diversion of faeces away from the large bowel of individuals with UC by creation of a temporary ileostomy. Conversely, it is also possible to induce diversion colitis in individuals with an ileostomy (Harig et al. 1989), which suggests removal of healthy microbes from the colon also has a detrimental effect. It is also now well documented that the gut microbiota populations of individuals with IBD are significantly altered compared to community controls (Manichanh et al. 2006; De Cruz et al. 2012; Rajilic-Stojanovic et al. 2013), adding further support for a role in causation. A key change is a reduced diversity, largely a result of a decrease in bacteria of the gram positive *Firmicutes* phylum, especially *Clostridium* clusters IV and XIV, whereas some bacteria belonging to the *Proteobacteriaceae*, particularly *E. coli* and *Enterobacteriaceae*, are increased in relative abundance. Other pathogens such as *Fusobacterium* sp., *Peptostreptococcus* sp., *Helicobacter* sp., *Campylobacter* sp. and *C. difficile* also tend to increase in number (Rajilic-Stojanovic et al. 2013).

Much of the diversity of the human gut microbiota seems to be a consequence of the need to use their enzymatic and metabolic machinery to breakdown and utilise the wide range of polysaccharides available to us as food. In the large bowel, the cells of the gut mucosa are reliant on fermentation by the resident bacteria to generate SCFA in order to maintain their integrity and function, and polysaccharides derived from the diet are the principal substrates for this. Of particular interest then, are the observations suggesting an altered microbial capacity to generate SCFA occurs in IBD (Galecka et al. 2013; Machiels et al. 2014). For example, significant reductions can be seen for the key butyrate producers *E. rectale*, *Roseburia* spp. (Rajilic-Stojanovic et al. 2013) and *F. prausnitzii*, the latter of which also has some other anti-inflammatory properties (Sokol et al. 2008). *R. bromii* plays an important role in the initial breakdown of dietary resistant starch (Abell et al. 2008), a substrate that is readily converted to SCFA, and reduced abundance of this species is also associated with UC (Rajilic-Stojanovic et al. 2013). Added to this, there are now a number of studies which have shown that treatments which increase butyrate in the large bowel can improve colitis symptoms using experimental animal models (Komiyama et al. 2011; Vieira et al. 2012; Le Leu et al. 2013). In humans, rectal administration of

butyrate has been shown to improve diversion colitis symptoms (Harig et al. 1989), helping to prevent atrophy of colonic tissues (Luceri et al. 2016).

Enteropathogenic microbes such as certain strains of *E. coli* and *Enterococcus* may contribute significantly to IBD and other gut conditions. In addition to the evidence of raised numbers in affected individuals there is experimental evidence to support such activities. To add weight to an important role for SCFA production, and the microbes which mediate this, in helping to protect against effects of these bacteria, the toxic effects of enterohaemorrhagic *E. coli* O157:H7 can be inhibited in vivo through increased production of acetate (Fukuda et al. 2011b). The acetate derived from bacteria of the genus *Bifidobacterium* was able to mediate this protection, suggesting potential for the use of appropriate strains as probiotics to treat conditions where *E. coli* or other similar pathogens contribute to disease. It is important to note that some strains of *E. coli* may benefit health e.g. by maintaining insulin-like growth factor signalling to muscle and preventing wasting associated with intestinal infections by certain pathogenic microbes (Schieber et al. 2015). Nevertheless, increasing numbers of gram negative bacteria such as *E. coli* can increase the risk of inflammation as components of their cell wall, lipopolysaccharide, promote inflammatory responses in tissues.

Despite numerous microbial species having been linked to IBD, it has not been possible to consistently pinpoint any particular microbes as a cause. It is quite likely that many gut microbes have the potential to trigger IBD under the right conditions, especially those where host defences, particular the mucus gut barrier, are weakened (Swidsinski et al. 2009). A large proportion of host immune defences reside within the gut to deal with the threat of luminal microbes invading the tissues. One of the first lines of defence is the mucus barrier which lines the gastrointestinal tract. Microbes are present within the outer layer of this mucus, and many use it as a nutritional substrate, but they are not normally present within the innermost layer. A breakdown of mucus barrier integrity is implicated in IBD, in part because the numbers of bacteria that contribute to large bowel mucus turnover have been shown to be altered in those with the disease, i.e. *A. muciniphila*, *Ruminococcus torques* and *Ruminococcus gnavus* (Png et al. 2010). Interestingly, some of these bacteria have also been found to be altered in the stool of children with autism spectrum disorder, who also often report a significant level of GI discomfort (Wang et al. 2011).

The maintenance of tight junctions between cells of the GI tract is also a critical line of defence by helping to prevent passage of unwanted microbes or molecules into host tissues. SCFA, but particularly butyrate, appear to play an important role in the maintenance of tight junctions (Fukuda et al. 2011b; Suzuki et al. 2008). A breakdown of this defence, a so-called 'leaky gut', may be a significant contributor to inflammation in IBD and is also linked to a growing number of other conditions (Michielan and D'Inca 2015). The recognition that a 'dysbiosis' of gut microbe populations is a likely contributor to IBD has recently led to the testing of a seemingly radical new treatment, faecal microbial transplantation (FMT), in which an individual receives stool donated by healthy individuals. It is hypothesised that the healthy complement of microbes will become established in the large bowel, promote re-establishment of tight junctions, a protective mucus lining, repopulate

the mucus layer with commensal bacteria and thereby curtail microbe-mediated inflammation. Although relatively unproven for treatment of IBD and other conditions where microbes contribute to the etiology, FMT is now firmly established as a successful means of treating *C. difficile* infections (which often resist all other known treatments) through rectal administration and through ingestion of capsules containing stool (Borody and Khoruts 2012; Mattila et al. 2012).

Gut microbes and their products also appear to play a role in the aetiology of colorectal cancer (CRC). Individuals with IBD have an elevated risk of CRC, suggesting that microbe-associated inflammation can contribute to oncogenesis. In otherwise healthy individuals there is a significantly greater risk of CRC when diets high in red or processed meat and low in fibre, which are typical of western style diets, are consumed (Norat et al. 2005; Murphy et al. 2012). A range of mechanisms has been proposed to explain this. Dietary protein can escape digestion and undergo fermentation in the large bowel, generating toxic by-products which can include ammonia, phenols, cresols, amines, and hydrogen sulphide (Windey et al. 2012). N-nitroso compounds (NOC) are alkylating agents which can also be produced from meat proteins by the action of gut microbes and have also been suggested as contributing to CRC through their ability to form DNA adducts in human colonic cells (Bingham et al. 1996). There is growing experimental evidence in animals and humans that consuming high levels of dietary protein, particularly as red meat, increases the level of DNA damage in the colon (which is regarded as a required step in oncogenesis) (Toden et al. 2007; Winter et al. 2011; Conlon et al. 2012; O'Callaghan et al. 2012; Le Leu et al. 2015). These studies also show that addition of fermentable dietary fibre to the diet in the form of resistant starch protects against this damage through mechanisms that appear to be at least partly mediated by the actions of SCFA produced by the microbiota. Gut microbes, including members of *Lactobacillus*, *Bifidobacterium* and *Bacteroides* genera, mediate secondary bile acid formation and turnover (Nicholson et al. 2012). These acids, particularly deoxycholic acid, are potentially carcinogenic and there is evidence that their levels are higher when SCFA levels are lower (Ou et al. 2012). Numerous species of gut microbes have been implicated in CRC, and these may act through a variety of mechanisms, such as the production of compounds like toxins or forms of reactive oxygen which damage tissues, or through exclusion of beneficial bacteria (Yu and Fang 2015). Some of the bacteria implicated include *Fusobacterium nucleatum*, invasive bacteria found to be strongly associated with the neoplastic tissues of CRC patients (Castellarin et al. 2012), *Bacteroides fragilis*, *Enterococcus faecalis*, *Helicobacter pylori* and *Streptococcus bovis* (Yu and Fang 2015).

6 Short Chain Fatty Acids, Inflammation and Allergy

The SCFA products of dietary fibre fermentation by the gut microbiota are pleiotropic metabolites that elicit their biological effects via both intra- and extra-cellular mechanisms. While un-ionized SCFA can cross cellular membranes by simple

diffusion, with pKa values of around 4.8, the majority of these acids exist in the ionised state at normal colonic pH. Therefore, most uptake of SCFA by the tissues of the colonic mucosa is facilitated by membrane bound transporter proteins. These include the low affinity/ high capacity transporters SLC16A1 (proton-coupled monocarboxylate transporter-1, MCT-1), SLC16A3 (MCT-3) and SLC16A7 (MCT-16) which are important when SCFA concentrations are relatively high and high affinity/ low capacity sodium-coupled monocarboxylate transporter-1 (SMCT-1; or SLC5A8) which are important when digesta and tissue SCFA concentrations are low. Low affinity receptors such as MCT-1 are distributed throughout the gut with expression highest in the large intestine of most mammals and reside on the apical (luminal) surface of the cell. In contrast, the high affinity transporter SMCT-1, which also promotes water absorption, is expressed on the apical epithelial membrane of the distal ileum and large intestine of mice, with expression highest in the colo-rectum (Iwanaga and Kishimoto 2015). SMCT-1 is also found on cells within the lamina propria (the tissue immediately below the mucosal layers) where SCFA, particularly butyrate, influences immune cells and enteric neurons (Vadivel et al. 2014). The relative affinity of SMCT-1 for its different SCFA substrates is: butyrate > propionate > lactate > acetate, which may contribute to its proposed tumour suppressor role (Ganapathy et al. 2005).

Past research has focused on the ability of SCFA to modulate biological responses by directly inhibiting histone deacetylases (HDACs) which results in increased histone acetylation and altered gene expression. The potent HDAC inhibitory effects of butyrate on the expression of genes that regulate proteins involved in cellular apoptosis, cell cycle regulation and DNA repair that may protect from colorectal oncogenesis (Fung et al. 2012) has received considerable attention, although HDAC inhibition may be SCFA and tissue specific. Acetate has recently been found to increase brain histone acetylation-state in rodents (Soliman and Rosenberger 2011). The effects on the immune response of SCFA on HDAC inhibition are largely anti-inflammatory (Tan et al. 2014) affecting not only cells of the innate immune system (Lin et al. 2015) but also increasing *Foxp3* gene expression and the numbers and immunosuppressive function of T regulatory cells in mice (Tao et al. 2007).

SCFA also modulate biological responses by activating G-protein-coupled receptors (GPCRs), mainly GPR41 (FFAR3), GPR43 (FFAR2) and GPR109A, which are expressed on the apical membrane of colonic epithelial and enteroendocrine cells (see reviews by Vadivel et al. 2014; Tan et al. 2014). GPR41 and GPR43 are activated by all three SCFA with propionate the most potent agonist for both GPR41 and GPR43, and with acetate more selective for GPR43 (Le Poul et al. 2003a). GPR109A is only activated by butyrate (Thangaraju et al. 2009) and is expressed in adipocytes, intestinal epithelial cells and some immune cells (see review by Singh et al. 2014). GPR43 was first described in neutrophils (Le Poul et al. 2003a) and has since been described in other immune cells, the gastrointestinal tract including endocrine L-cells of the ileum and colon producing intestinal peptide YY (PYY) and glucagon-like peptide 1 (GLP-1) (Tolhurst et al. 2012). GPR41 is more broadly expressed in a number of tissues (Le Poul et al. 2003b).

The gut intestinal barrier consists of a layer of epithelial cells and products including mucus, immunoglobulins and other antimicrobial agents and microbes that interact to provide a selective barrier to protect the host. The barrier enables the uptake of water, electrolytes, nutrients and other molecules while preventing the entry of antigens and microorganisms (Camilleri et al. 2012). The epithelium forms the main physical barrier between the gut lumen and the mucosal tissues with absorption occurring either transcellularly by active transport or passive diffusion, or through the paracellular spaces between the cells by passive movement. The selective paracellular barrier is maintained by three adhesive protein complexes: desmosomes, adherens junctions, and tight junctions (Groschwitz and Hogan 2009). The tight junctions seal the intercellular space and involve claudins and occludins that form the paracellular pore, and scaffold and other cytoplasmic proteins including zonula occludens (ZO-1, 2 and 3).

Intestinal barrier dysfunction enabling gut translocation of bacteria causing inflammation and autoimmune disease has also been suggested as a causative factor in a range of diseases including irritable bowel syndrome (Piche 2014; Vivinus-Nebot et al. 2014), inflammatory bowel disease (Michielan and D’Inca 2015; Ploger et al. 2012) (IBD), food allergies (Perrier and Corthesy 2011), celiac disease, asthma (Hijazi et al. 2004) and types 1 (T1D) and 2 (T2D) diabetes (de Kort et al. 2011). Butyrate, but not acetate, decreased bacterial translocation in cell models (Lewis et al. 2010) and enhanced intestinal barrier function in vitro by modifying the expression of the tight junction protein Claudin-1 (Wang et al. 2012). Elsewhere, acetate has been shown to enhance gut barrier function and protect mice treated with *E. coli* O157:H7 from translocation of Shiga toxin from the gut lumen (Fukuda et al. 2011a).

Impaired tight junction function has been found in patients with Crohn’s disease (Zeissig et al. 2007) (CD) and ulcerative colitis (Heller et al. 2005) (UC) and first degree relatives of patients with Crohn’s disease have increased intestinal permeability (Peeters et al. 1997). Paracellular permeability is increased in patients with quiescent IBD and IBS-like symptoms associated with persistent subclinical intestinal inflammation (Vivinus-Nebot et al. 2014). Butyrate-producing bacteria are reduced in the faeces of CD (Takahashi et al. 2016) and UC (Machiels et al. 2013) patients compared to healthy controls. The physical and chemical protective mucus layer is thinner and more variable in thickness in UC disease patients (Pullan et al. 1994); in rodents, diets containing resistant starch delivering high concentrations of butyrate to the large bowel increased mucus thickness (Toden et al. 2014). However, the use of butyrate enemas to control or maintain relapse in IBD patients has had mixed results (Breuer et al. 1997; Scheppach 1996; Steinhart et al. 1996; Hamer et al. 2010) which may be due to difficulty maintaining prolonged mucosal contact. Butyrate metabolism is impaired in the inflamed mucosa of IBD patients, which may be due to a reduction in butyrate uptake due to a downregulation of the MCT-1 butyrate transporter in IBD (Thibault et al. 2007), leading to the suggestion that butyrate deficiency is a causative factor for the inflammation (Thibault et al. 2010). Butyrate delivered to the colon by butyrylated starch

ameliorated colitis in an adoptive transfer mouse model whereas starches delivering acetate and propionate had no protective effect (Furusawa et al. 2013).

Increased gastric and small intestinal permeability precedes the development of diabetes in the BB rat (Meddings et al. 1999) and increased permeability resulting in autoimmune destruction of the pancreatic beta cells may play a role in the development of diabetes. Furthermore, glucagon-like peptide-2 (GLP-2), an enteroendocrine peptide involved with satiety control released in response to the ingestion of a prebiotic, improves barrier function and reduces LPS concentrations in mice (Cani et al. 2009). Dietary resistant starch (RS) provides substrate for colonic fermentation and the production of SCFA. These diets are associated with improved bowel health, reduced abdominal fat and improved insulin sensitivity and increased serum GLP-1 is likely to play a role in mediating these effects (Keenan et al. 2015). Diets providing high levels of colonic SCFA may have potential to improve metabolic control in type 2 diabetes (Puddu et al. 2014).

SCFA have been shown to affect the immune system through multiple mechanisms that contribute to colonic health and homeostasis (see reviews by (Tan et al. 2014; Fung et al. 2014; Vinolo et al. 2011b). These mechanisms include modulating chemotaxis and the activity of macrophages and neutrophils (Maslowski et al. 2009; Vinolo et al. 2011a); the production of reactive oxygen species by neutrophils (Maslowski et al. 2009); suppressing pro-inflammatory and inhibiting anti-inflammatory cytokine production by macrophages and neutrophils (TNF- α , IL-2, IL-6 and IL-10), the interaction of neutrophils with endothelial epithelium (Vinolo et al. 2009); and modulating NF-KB activity by inhibition of HDAC activity (Inan et al. 2000).

SCFA also induce T_{reg} cells from naive CD4+ T-cell precursors in the colonic lamina propria by inhibiting histone deacetylases and facilitating *Foxp3* expression (Furusawa et al. 2013, Arpaia et al. 2013). SCFA have been shown to expand the existing T_{reg} cell pool via a GPR43-dependent mechanism (Smith et al. 2013). T_{reg} cells have an important role moderating allergic and inflammatory responses (Sakaguchi et al. 2008) and may also be induced through the production of TGF β 1 by *Clostridia* species from clusters IV, XIVa, and XVIII (Atarashi et al. 2013). In addition, butyrate promotes anti-inflammatory properties in macrophages and dendritic cells in the colonic lamina propria and enables them to induce differentiation of IL-10-producing T_{reg} cells via GPR109A signaling (Singh et al. 2014).

The route of administration may determine the effects of SCFA. When individual SCFA are administered by drinking water they are largely absorbed in the small intestine and acetate and propionate delivered by this route are more effective at accumulating colonic T_{reg}s than butyrate, suggesting acid absorbed in the small intestine may be important for migration of T_{reg} cells into the colon from lymphoid tissues (Smith et al. 2013). Butyrate delivered in the drinking water increased peripheral but not thymic or colonic Treg cells, whereas butyrate delivered by enema increased Treg numbers in the colonic lamina propria (Arpaia et al. 2013). Likewise, butyrate delivered lumenally to the colon via butyrylated starch induced colonic Treg differentiation but propionate delivered from propionylated starch was less effective and acetate from acetylated starch had no effect (Furusawa et al. 2013).

The anti-inflammatory effects of acetate administered in drinking water have been demonstrated in animal models of colitis, arthritis and asthma. Acetate ameliorated disease symptoms implying a major role for the acetate-GPR43 axis (Maslowski et al. 2009). Rodent studies suggest a maternal diet high in acetate may reduce the incidence of asthma in offspring by influencing the expression of certain genes in the fetal lung (Thorburn et al. 2015).

Early studies showed that SCFA are rapidly taken up in the large bowel with the absorption of sodium and chloride (Rajendran and Binder 1994) and with the secretion of bicarbonate (Fleming et al. 1991). SCFA have since been shown to induce the activity of sodium-hydrogen exchange transporters (NHE) in intestinal cells that promote the absorption of fluid and Na-H , SCFA-HCO_3^- and Cl-SCFA exchanges (see review Binder 2010). Multiple isoforms of NHEs have been identified in intestinal epithelial cells but the activity of NHE3 (Musch et al. 2001) is increased by SCFA and with NHE2 is found in the small and large intestine of humans (Hoogerwerf et al. 1996). Butyrate also stimulates intestinal NHE8 expression enhancing sodium uptake in vitro (Xu et al. 2015). The transport protein(s) responsible for SCFA-HCO_3^- exchange have not been described (Binder 2010) although a low-affinity, high capacity butyrate- HCO_3^- process and a high affinity, low-capacity proton-monocarboxylate co-transporter have been described (Lecona et al. 2008).

Unlike several other intestinal transport processes, SCFA-stimulated absorption of fluid and electrolytes is not inhibited by mucosal cAMP (Ramakrishna et al. 1990). Mucosal cAMP is produced in response to enterotoxins secreted by many bacterial pathogens responsible for acute infectious diarrhoea, including *Vibrio cholera* (Kimberg et al. 1971), *S. typhimurium*, *Shigella dysenteriae* type 1 toxin, *Campylobacter jejuni* (see review by Binder 2009). Butyrate has been found to restore the activities of NHE2 and 3 isoforms inhibited by cAMP in vitro (Subramanya et al. 2007) and also decrease by 40 % the cholera-toxin induced increase in cAMP (Subramanya et al. 2007). Hence, delivering SCFA to the colon has potential to reduce fluid and electrolyte loss and improve the clinical response to oral rehydration solution (ORS) in patients with acute infectious diarrhoea.

SCFA can be produced in the colon by the fermentation of ingested RS, and RS added to ORS promotes fluid and electrolyte uptake in a perfused-gut rat model of cholera-toxin (CT) diarrhoea (Subramanya et al. 2006). It also reduces fluid loss and recovery time in human adults (Ramakrishna et al. 2000) and duration of diarrhoea in children (Raghupathy et al. 2006). Acylated starches are largely resistant to small intestinal digestion and deliver specific SCFA rapidly to the large bowel (Clarke et al. 2008, 2011c). Acetylated starch was more effective at promoting fluid and electrolyte uptake than RS or acylated starch delivering propionate or butyrate in the perfused-gut rat CT model (Clarke et al. 2011a). This may be the result of more rapid and complete release of bound acetate resulting from the more disrupted starch structure compared to starches acylated with propionate and butyrate. The acetylated starch shortened the duration of diarrhoea in patients with acute infectious diarrhoea (Pal et al. 2013) but not faecal volume.

7 Future Prospects

Modern techniques in metagenomics analysis continue to dramatically enhance our understanding of how microbial taxonomy and the genetic potential of the human microbiota change in health and disease and how they respond to changing environmental conditions such as diet. However, this is only part of the equation. Understanding how the function of the microbiota changes, how this impacts on the health and wellbeing of the host and what levers can be pulled to efficiently shape the microbiome and its function for improved health will be important areas for future research.

Dietary fibre provides a glimpse into the multifaceted impacts that food and xenobiotics can have on the microbiota and the host, and highlights the importance of small molecule metabolites as mediators of change. As discussed above, provision of a fermentable substrate alone provides a growth advantage to bacteria in the gut ecosystem capable of metabolizing these substrates. Selective pressure within the gut microbial population is further modified by changes in the chemical environment caused by the accumulation of the metabolic end products of fermentation. Dropping digesta pH resulting from the accumulation of SCFA further advantages some microbes over others while the SCFA themselves, pleiotropic bioactive agents in their own right, provide vehicles to the host for energy salvage, immunological signaling, promotion of gut homeostasis and repair, motility modification, cellular signaling (both via GPCRs and histone deacetylase inhibition) and satiety promotion. But fibre is just one dietary substrate capable of modifying the gut microbial structure and function. Other macronutrients entering the colon can also promote the growth of other bacterial populations leading to the production of other metabolites with different outcomes for other microbes and the host. Yet other dietary molecules or phytonutrients may alternatively act by modifying the efficiency of other microbial processes e.g. the inhibition of RS fermentation efficiency by cutins and waxes (Edwards et al. 2012).

The human metabolome is very complex. Lipids alone have been estimated to have the potential to generate 9000–10,000 different molecular species (Yetukuri et al. 2008). With the gut microbiome carrying around 40 times the number of protein coding genes as the human genome, it is likely that the metabolome produced by the gut microflora will be substantially more complex. While SCFA are undoubtedly interesting and important metabolites, there are many other gut metabolites of microbe, host or dietary origin, both known and yet to be identified, that are capable of eliciting potent physiological effects. These include quorum sensing and virulence factors that regulate the composition of the surrounding microbiota as well as metabolites modulating host functions including the gut immune system (Nicholson et al. 2005, 2012).

The challenge will be to bring together our growing understanding of factors affecting the gut microbiome and the extent and variation in the gut metabolome with knowledge of the associated impacts on host physiology to develop predictive personalized approaches to health management and chronic disease prevention. But

there remains much to be done. Expanding our knowledge of the gut microbiome and its metabolic potential will be important. Only some 10 % of the currently sequenced open reading frames in the microbiome are recognized as encoding proteins with an assignable or predicted structural or enzymatic function. Further our understanding of the metabolome is in its infancy while attribution of the physiological impacts of metabolites continues to be assessed on a candidate by candidate basis (Martin et al. 2007). While there is much important work to be done in the expansion of these individual catalogues (genes, their function; metabolites and their impact on physiology) there is now a real need to bring these areas closer together. With the increasing use of high resolution spectroscopy methods to analyse metabolite profiles of microbial origin, opportunities now exist to statistically integrate large and complex metabolic and metagenomic data sets, using informatics to reveal pathways and putative functional relationships previously inaccessible. However, validation of these proposed relationships will be crucial. In this regard, the development of improved in vitro fermentation systems that more accurately represent the processes occurring in the gut digesta and the availability of gut organoid culture systems that accurately recapitulate biological responses of the gut mucosa to bioactive metabolites are providing an exciting prospect of a medium throughput screening of these in silico predictions en route to more classical animal and human substantiation of the strongest candidates. While we are only in the early stages of this new, data-driven revolution, if it lives up to its promise then the path to a more detailed understanding of the gut, its metabolites and their impact on human health becomes clearer and the promise of translating this knowledge to help inform the personalization of health care, a tangible and exciting prospect.

References

- Abell GC, Cooke CM, Bennett CN, Conlon MA, Mcorist AL (2008) Phylotypes related to *Ruminococcus bromii* are abundant in the large bowel of humans and increase in response to a diet high in resistant starch. *FEMS Microbiol Ecol* 66:505–515
- Abell GCJ, Christophersen CT, McOrist AL, Clarke JM (2011) Dietary resistant and butyrylated starches have different effects on the faecal bacterial flora of azoxymethane-treated rats. *Br J Nutr* 105:1480–1485
- Agbenorhevi JK, Kontogiorgos V, Kirby AR, Morris VJ, Tosh SM (2011) Rheological and microstructural investigation of oat beta-glucan isolates varying in molecular weight. *Int J Biol Macromol* 49:369–377
- Australian Institute of Health and Welfare & Australasian Association of Cancer Registries (AIHW) (2012) Cancer in Australia: an overview, 2012 Cancer Series No. 74. Cat. No. CAN 70
- Alam MZ, Alam Q, Kamal MA, Abuzenadah AM, Haque A (2014) A possible link of gut microbiota alteration in type 2 diabetes and alzheimer's disease pathogenicity: an update. *CNS Neurol Disord-Drug Targets* 13:383–390
- Anderson IH, Levine AS, Levitt MD (1981) Incomplete absorption of the carbohydrate in all-purpose wheat-flour. *N Engl J Med* 304:891–892

- Arpaia N, Campbell C, Fan X, Dikij S, van der Veeken J, Deroos P, Liu H, Cross JR, Pfeffer K, Coffey PJ, Rudensky AY (2013) Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. *Nature* 504:451–455
- Arrigoni E (2001) Enzymatic modification of dietary fiber sources. Marcel Dekker Inc, New York
- Atarashi K, Tanoue T, Oshima K, Suda W, Nagano Y, Nishikawa H, Fukuda S, Saito T, Narushima S, Hase K, Kim S, Fritz JV, Wilmes P, Ueha S, Matsushima K, Ohno H, Olle B, Sakaguchi S, Taniguchi T, Morita H, Hattori M, Honda K (2013) Treg induction by a rationally selected mixture of Clostridia strains from the human microbiota. *Nature* 500:232–236
- Bach Knudsen KE (2015) Microbial degradation of whole-grain complex carbohydrates and impact on short-chain fatty acids and health. *Adv Nutr* (Bethesda, Md.) 6:206–213
- Backhed F, Roswall J, Peng YQ, Feng Q, Jia HJ, Kovatcheva-Datchary P, Li Y, Xia Y, Xie HL, Zhong HZ, Khan MT, Zhang JF, Li JH, Xiao L, Al-Aama J, Zhang DY, Lee YS, Kotowska D, Colding C, Tremaroli V, Yin Y, Bergman S, Xu X, Madsen L, Kristiansen K, Dahlgren J, Jun W (2015) Dynamics and stabilization of the human gut microbiome during the first year of life. *Cell Host Microbe* 17:690–703
- Backman RV (2009) The effects of plantain non-starch polysaccharide upon the gut bacteria. Ph. D., University of Aberdeen, UK
- Baghurst PA, Baghurst KI, Record SJ (1996) Dietary fibre, non-starch polysaccharides and resistant starch—a review. *Food Aust* 48:S3–S35
- Barrett E, Ross RP, O'Toole PW, Fitzgerald GF, Stanton C (2012) γ -Aminobutyric acid production by culturable bacteria from the human intestine. *J Appl Microbiol* 113:411–417
- Binder HJ (2009) Mechanisms of diarrhea in inflammatory bowel diseases. *Ann NY Acad Sci* 1165:285–293
- Binder HJ (2010) Role of colonic short-chain fatty acid transport in diarrhea. *Annu Rev Physiol* 72:297–313
- Bingham SA, Pignatelli B, Pollock JRA, Ellul A, Malaveille C, Gross G, Runswick S, Cummings JH, O'Neill IK (1996) Does increased endogenous formation of N-nitroso compounds in the human colon explain the association between red meat and colon cancer? *Carcinogenesis* 17:515–523
- Bird AR (2007) Dietary fibre, health and chronic disease. *Diab Manage J* 12
- Bird AR, Brown IL, Topping DL (2000) Starches, resistant starches, the gut microflora and human health. *Curr Issues Intest Microbiol* 1:25–37
- Bird AR, Conlon MA, Christophersen CT, Topping DL (2010) Resistant starch, large bowel fermentation and a broader perspective of prebiotics and probiotics. *Benef Microbes* 1:423–431
- Bird AR, Topping DL (2001) Resistant starches, fermentation, and large bowel health. Marcel Dekker Inc, New York
- Bird AR, Usher S, May B, Topping DL, Morell MK (2012) Resistant starch measurement, intakes, and dietary targets. CRC Press, Taylor & Francis Group, Boca Raton
- Borody TJ, Khoruts A (2012) Fecal microbiota transplantation and emerging applications. *Nat Rev Gastroenterol Hepatol* 9:88–96
- Breuer RI, Soergel KH, Lashner BA, Christ ML, Hanauer SB, Vanagunas A, Harig JM, Keshavarzian A, Robinson M, Sellin JH, Weinberg D, Vidican DE, Flemal KL, Rademaker AW (1997) Short chain fatty acid rectal irrigation for left-sided ulcerative colitis: a randomised, placebo controlled trial. *Gut* 40:485–491
- Broekaert WF, Courtin CM, Verbeke K, van de Wiele T, Verstraete W, Delcour JA (2011) Prebiotic and other health-related effects of cereal-derived arabinoxylans, arabinoxylan-oligosaccharides, and xylooligosaccharides. *Crit Rev Food Sci Nutr* 51:178–194
- Brouns F, Kettlitz B, Arrigoni E (2002) Resistant starch and “the butyrate revolution”. *Trends Food Sci Technol* 13:251–261
- Brownlee I (2014) The impact of dietary fibre intake on the physiology and health of the stomach and upper gastrointestinal tract. *Bioact Carbohydr Diet Fibre* 4:155–169
- Burkitt DP (1973) Some diseases characteristic of modern western civilization. *Br Med J* 1:274–278
- Buttriss JL, Stokes CS (2008) Dietary fibre and health: an overview. *Nutr Bull* 33:186–200

- Camilleri M, Madsen K, Spiller R, Greenwood-van Meerveld B, Verne GN (2012) Intestinal barrier function in health and gastrointestinal disease. *Neurogastroenterol Motil* 24:503–512
- Cani PD, Possemiers S, van de Wiele T, Guiot Y, Everard A, Rottier O, Geurts L, Naslain D, Neyrinck A, Lambert DM, Muccioli GG, Delzenne NM (2009) Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. *Gut* 58:1091–1103
- Castellarin M, Warren RL, Freeman JD, Dreolini L, Krzywinski M, Strauss J, Barnes R, Watson P, Allen-Vercoe E, Moore RA, Holt RA (2012) *Fusobacterium nucleatum* infection is prevalent in human colorectal carcinoma. *Genome Res* 22:299–306
- Cats A, Devries EGE, Mulder NH, Kleibeuker JH (1996) Regional differences of physiological functions and cancer susceptibility in the human large intestine. *Int J Oncol* 9:1055–1069
- Cerutti A (2008) The regulation of IgA class switching. *Nat Rev Immunol* 8:421–434
- Chung HC, Pamp SJ, Hill JA, Surana NK, Edelman SM, Troy EB, Reading NC, Villablanca EJ, Wang S, Mora JR, Umesaki Y, Mathis D, Benoist C, Relman DA, Kasper DL (2012) Gut immune maturation depends on colonization with a host-specific microbiota. *Cell* 149:1578–1593
- Claesson MJ, Jeffery IB, Conde S, Power SE, O'Connor EM, Cusack S, Harris HMB, Coakley M, Lakshminarayanan B, O'Sullivan O, Fitzgerald GF, Deane J, O'Connor M, Harnedy N, O'Connor K, O'Mahony D, van Sinderen D, Wallace M, Brennan L, Stanton C, Marchesi JR, Fitzgerald AP, Shanahan F, Hill C, Ross RP, O'Toole PW (2012) Gut microbiota composition correlates with diet and health in the elderly. *Nature* 488:178
- Clarke JM, Dharmalingam T, Srinivasan P, Young GP, Lockett TJ, Ramakrishna BS (2011a) Acetylated high amylose maize starch improves the efficacy of oral rehydration solution in a rat model of cholera. *Gastroenterology* 140:S134
- Clarke JM, Topping DL, Bird AR, Young GP, Cobiac L (2008) Effects of high amylose maize starch and butyrylated high amylose maize starch on azoxymethane-induced intestinal cancer in rats. *Carcinogenesis* 29:2190–2194
- Clarke JM, Topping DL, Christophersen CT, Bird AR, Lange K, Saunders I, Cobiac L (2011b) Butyrate esterified to starch is released in the human gastrointestinal tract. *Am J Clin Nutr* 94:1276–1283
- Clarke JM, Topping DL, Christophersen CT, Bird AR, Lange K, Saunders I, Cobiac L (2011c) Butyrate esterified to starch is released in the human gastrointestinal tract. *Am J Clin Nutr* 94:1276–1283
- Clemente JC, Ursell LK, Parfrey LW, Knight R (2012) The impact of the gut microbiota on human health: an integrative view. *Cell* 148:1258–1270
- CODEX (2010) Joint FAO/WHO food standards programme. In: *Alimentarius* (ed) Secretariat of the Codex Alimentarius Commission: CODEX guidelines on nutrition labeling CAC/GL 2–1985 as last amended 2010
- Collier CT, Hofacre CL, Payne AM, Anderson DB, Kaiser P, Mackie RI, Gaskins HR (2008) *Coccidia*-induced mucogenesis promotes the onset of necrotic enteritis by supporting *Clostridium perfringens* growth. *Vet Immunol Immunopathol* 122:104–115
- Comino P, Collins H, Lahnstein J, Gidley MJ (2016) Effects of diverse food processing conditions on the structure and solubility of wheat, barley and rye endosperm dietary fibre. *J Food Eng* 169:228–237
- Conlon MA, Bird AR (2015) The impact of diet and lifestyle on gut microbiota and human health. *Nutrients* 7:17–44
- Conlon MA, Kerr CA, McSweeney CS, Dunne RA, Shaw JM, Kang S, Bird AR, Morell MK, Lockett TJ, Molloy PL, Regina A, Toden S, Clarke JM, Topping DL (2012) Resistant starches protect against colonic DNA damage and alter microbiota and gene expression in rats fed a Western diet. *J Nutr* 142:832–840
- Costabile A, Kolida S, Klinder A, Gietl E, Bauerlein M, Froberg C, Landschutze V, Gibson GR (2010) A double-blind, placebo-controlled, cross-over study to establish the bifidogenic effect of a very-long-chain inulin extracted from globe artichoke (*Cynara scolymus*) in healthy human subjects. *Br J Nutr* 104:1007–1017

- Cummings JH, Bingham SA, Heaton KW, Eastwood MA (1992) Fecal weight, colon cancer risk, and dietary-intake of nonstarch polysaccharides (dietary fiber). *Gastroenterology* 103:1783–1789
- Cummings JH, Stephen AM (2007) Carbohydrate terminology and classification. *Eur J Clin Nutr* 61:S5–S18
- Dahl WJ, Stewart ML (2015) Position of the academy of nutrition and dietetics: health implications of dietary fiber. *J Acad Nutr Diet* 115:1861–1870
- Davis LM, Martinez I, Walter J, Goin C, Hutkins RW (2011) Barcoded pyrosequencing reveals that consumption of galactooligosaccharides results in a highly specific bifidogenic response in humans. *PLoS One* 6:e25200
- De Cruz P, Kang S, Wagner J, Buckley M, Sim WH, Prideaux L, Lockett T, McSweeney C, Morrison M, Kirkwood CD, Kamm MA (2015) Association between specific mucosa-associated microbiota in Crohn's disease at the time of resection and subsequent disease recurrence: a pilot study. *J Gastroenterol Hepatol* 30:268–278
- de Cruz P, Prideaux L, Wagner J, Ng SC, McSweeney C, Kirkwood C, Morrison M, Kamm MA (2012) Characterization of the gastrointestinal microbiota in health and inflammatory bowel disease. *Inflamm Bowel Dis* 18:372–390
- de Kort S, Keszthelyi D, Masclee AA (2011) Leaky gut and diabetes mellitus: what is the link? *Obes Rev* 12:449–458
- de Menezes EW, Giuntini EB, Dan MCT, Sarda FAH, Lajolo FM (2013) Codex dietary fibre definition—justification for inclusion of carbohydrates from 3 to 9 degrees of polymerisation. *Food Chem* 140:581–585
- Deng YY, Misselwitz B, Dai N, Fox M (2015) Lactose intolerance in adults: biological mechanism and dietary management. *Nutrients* 7:8020–8035
- Djouzi A, Andrieux C (1997) Compared effects of three oligosaccharides on metabolism of intestinal microflora in rats inoculated with a human faecal flora. *Br J Nutr* 78:313–324
- Dominguez-Bello MG, Costello EK, Contreras M, Magris M, Hidalgo G, Fierer N, Knight R (2010) Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proc Natl Acad Sci USA* 107:11971–11975
- Eaton SB (2006) The ancestral human diet: what was it and should it be a paradigm for contemporary nutrition? *Proc Nutr Soc* 65:1–6
- Edwards CA, Garcia AL, Combet E (2012) Colonic metabolism of bioactive molecules potential impact of dietary fiber. CRC Press, Taylor & Francis Group, Boca Raton
- Edwards CA, Xie CR, Garcia AL (2015) Dietary fibre and health in children and adolescents. *Proc Nutr Soc* 74:292–302
- Elsden SR, Hitchcock MWS, Marshall RA, Phillipson AT (1946) Volatile acid in the digesta of ruminants and other animals. *J Exp Biol* 22:191–202
- Englyst H, Wiggins HS, Cummings JH (1982) Determination of the non-starch polysaccharides in plant foods by gas-liquid-chromatography of constituent sugars as alditol acetates. *Analyst* 107:307–318
- Englyst K, Quigley M, Englyst H, Parmar B, Damant A, Elahi S, Lawrance P (2013) Evaluation of methods of analysis for dietary fibre using real foods and model foods. *Food Chem* 140:568–573
- Englyst KN, Liu S, Englyst HN (2007) Nutritional characterization and measurement of dietary carbohydrates. *Eur J Clin Nutr* 61:S19–S39
- Eswaran S, Muir J, Chey WD (2013) Fiber and functional gastrointestinal disorders. *Am J Gastroenterol* 108:718–727
- Favier CF, Vaughan EE, de Vos WM, Akkermans ADL (2002) Molecular monitoring of succession of bacterial communities in human neonates. *Appl Environ Microbiol* 68:219–226
- Fleming SE, Choi SY, Fitch MD (1991) Absorption of short-chain fatty acids from the rat cecum in vivo. *J Nutr* 121:1787–1797
- Flint HJ, Scott KP, Louis P, Duncan SH (2012) The role of the gut microbiota in nutrition and health. *Nat Rev Gastroenterol Hepatol* 9:577–589

- Frank DN, St Amand AL, Feldman RA, Boedeker EC, Harpaz N, Pace NR (2007) Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. *Proc Natl Acad Sci USA* 104:13780–13785
- Fukuda S, Toh H, Hase K, Oshima K, Nakanishi Y, Yoshimura K, Tobe T, Clarke JM, Topping DL, Suzuki T, Taylor TD, Itoh K, Kikuchi J, Morita H, Hattori M, Ohno H (2011a) Bifidobacteria can protect from enteropathogenic infection through production of acetate. *Nature* 469:543–547
- Fukuda S, Toh H, Hase K, Oshima K, Nakanishi Y, Yoshimura K, Tobe T, Clarke JM, Topping DL, Suzuki T, Taylor TD, Itoh K, Kikuchi J, Morita H, Hattori M, Ohno H (2011b) Bifidobacteria can protect from enteropathogenic infection through production of acetate. *Nature* 469:543–547
- Fung KY, Cosgrove L, Clarke J, Lockett T, Morita T, Hase K, Topping DL (2014) Large bowel short chain fatty acid production, immune status and immune cell function: implications for chronic inflammatory disease. Nova Science Publishers, New York
- Fung KY, Ooi CC, Lewanowitsch T, Tan S, Tan HT, Lim TK, Lin Q, Williams DB, Lockett TJ, Cosgrove LJ, Chung MC, Head RJ (2012) Identification of potential pathways involved in induction of apoptosis by butyrate and 4-benzoylbutyrate in HT29 colorectal cancer cells. *J Proteome Res* 11:6019–6029
- Furusawa Y, Obata Y, Fukuda S, Endo TA, Nakato G, Takahashi D, Nakanishi Y, Uetake C, Kato K, Kato T, Takahashi M, Fukuda NN, Murakami S, Miyauchi E, Hino S, Atarashi K, Onawa S, Fujimura Y, Lockett T, Clarke JM, Topping DL, Tomita M, Hori S, Ohara O, Morita T, Koseki H, Kikuchi J, Honda K, Hase K, Ohno H (2013) Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature* 504:446–450
- Galecka M, Szachta P, Bartnicka A, Lykowska-Szuber L, Eder P, Schwiertz A (2013) *Faecalibacterium prausnitzii* and Crohn's disease—is there any connection? *Pol J Microbiol* 62:91–95
- Gallo RL, Hooper LV (2012) Epithelial antimicrobial defence of the skin and intestine. *Nat Rev Immunol* 12:503–516
- Ganapathy V, Gopal E, Miyauchi S, Prasad PD (2005) Biological functions of SLC5A8, a candidate tumour suppressor. *Biochem Soc Trans* 33:237–240
- Garrett WS (2015) Cancer and the microbiota. *Science* 348:80–86
- Gevers D, Kugathasan S, Denson LA, Vazquez-Baeza Y, van Treuren W, Ren B, Schwager E, Knights D, Song SJ, Yassour M, Morgan XC, Kostic AD, Luo C, Gonzalez A, McDonald D, Haberman Y, Walters T, Baker S, Rosh J, Stephens M, Heyman M, Markowitz J, Baldassano R, Griffiths A, Sylvester F, Mack D, Kim S, Crandall W, Hyams J, Huttenhower C, Knight R, Xavier RJ (2014) The treatment-naïve microbiome in new-onset Crohn's disease. *Cell Host Microbe* 15:382–392
- Gibson GR, Probert HM, Van Loo J, Rastall RA, Roberfroid MB (2004) Dietary modulation of the human colonic microbiota: updating the concept of prebiotics. *Nutr Res Rev* 17:259–275
- Gibson GR, Roberfroid MB (1995) Dietary modulation of the human colonic microbiota—introducing the concept of prebiotics. *J Nutr* 125:1401–1412
- Goldman SM, Kamel F, Ross GW, Jewell SA, Marras C, Hoppin JA, Umbach DM, Bhudhikanok GS, Meng C, Korell M, Comyns K, Hauser RA, Jankovic J, Factor SA, Bressman S, Lyons KE, Sandler DP, Langston JW, Tanner CM (2014) Peptidoglycan recognition protein genes and risk of Parkinson's disease. *Mov Disord* 29:1171–1180
- Grembecka M (2015) Sugar alcohols-their role in the modern world of sweeteners: a review. *Eur Food Res Technol* 241:1–14
- Groschwitz KR, Hogan SP (2009) Intestinal barrier function: molecular regulation and disease pathogenesis. *J Allergy Clin Immunol* 124:3–20 (quiz 21–2)
- Group NHW, Peterson J, Garges S, Giovanni M, McInnes P, Wang L, Schloss JA, Bonazzi V, McEwen JE, Wetterstrand KA, Deal C, Baker CC, di Francesco V, Howcroft TK, KARP RW, Lunsford RD, Wellington CR, Belachew T, Wright M, Giblin C, David H, Mills M, Salomon R, Mullins C, Akolkar B, Begg L, Davis C, Grandison L, Humble M, Khalsa J,

- Little AR, Peavy H, Pontzer C, Portnoy M, Sayre MH, Starke-Reed P, Zakhari S, Read J, Watson B, Guyer M (2009) The NIH human microbiome project. *Genome Res* 19:2317–2323
- Haenen D, Zhang J, Souza da Silva C, Bosch G, van der Meer IM, van Arkel J, van den Borne JJ, Perez Gutierrez O, Smidt H, Kemp B, Muller M, Hooiveld GJ (2013) A diet high in resistant starch modulates microbiota composition, SCFA concentrations, and gene expression in pig intestine. *J Nutr* 143:274–283
- Halmos EP, Christophersen CT, Bird AR, Shepherd SJ, Gibson PR, Muir JG (2015) Diets that differ in their FODMAP content alter the colonic luminal microenvironment. *Gut* 64:93–100
- Hamer HM, Jonkers DMAE, Vanhoutvin SALW, Troost FJ, Rijkers G, de Bruine A, Bast A, Venema K, Brummer RJM (2010) Effect of butyrate enemas on inflammation and antioxidant status in the colonic mucosa of patients with ulcerative colitis in remission. *Clin Nutr* 29: 738–744
- Harig JM, Soergel KH, Komorowski RA, Wood CM (1989) Treatment of diversion colitis with short-chain fatty-acid irrigation. *N Engl J Med* 320:23–28
- Haro C, Garcia-Carpintero S, Alcalá-Díaz JF, Gomez-Delgado F, Delgado-Lista J, Perez-Martinez P, Zuniga OAR, Quintana-Navarro GM, Landa BB, Clemente JC, Lopez-Miranda J, Camargo A, Perez-Jimeanez F (2016) The gut microbial community in metabolic syndrome patients is modified by diet. *J Nutr Biochem* 27:27–31
- Heller F, Florian P, Bojarski C, Richter J, Christ M, Hillenbrand B, Mankertz J, Gitter AH, Burgel N, Fromm M, Zeitz M, Fuss I, Strober W, Schulzke JD (2005) Interleukin-13 is the key effector Th2 cytokine in ulcerative colitis that affects epithelial tight junctions, apoptosis, and cell restitution. *Gastroenterology* 129:550–564
- Heneker T, Edwards CA, Preston T (1998) Digestion and colonic fermentation of maize porridge using a $^{13}\text{CO}_2$ breath test. *South African Congress of Gastroenterology*
- Hijazi Z, Molla AM, Al-Habashi H, Muawad WM, Molla AM, Sharma PN (2004) Intestinal permeability is increased in bronchial asthma. *Arch Dis Child* 89:227–229
- Hoogerwerf WA, Tsao SC, Devuyt O, Levine SA, Yun CH, Yip JW, Cohen ME, Wilson PD, Lazenby AJ, Tse CM, Donowitz M (1996) NHE2 and NHE3 are human and rabbit intestinal brush-border proteins. *Am J Physiol* 270:G29–G41
- Hou JK, Abraham B, El-Serag H (2011) Dietary intake and risk of developing inflammatory bowel disease: a systematic review of the literature. *Am J Gastroenterol* 106:563–573
- Huttenhower C, Gevers D, Knight R, Abubucker S, Badger JH, Chinwalla AT, Creasy HH, Earl AM, Fitzgerald MG, Fulton RS, Giglio MG, Hallsworth-Pepin K, Lobos EA, Madupu R, Magrini V, Martin JC, Mitreva M, Muzny DM, Sodergren EJ, Versalovic J, Wollam AM, Worley KC, Wortman JR, Young SK, Zeng QD, Aagaard KM, Abolude OO, Allen-Vercoe E, Alm EJ, Alvarado L, Andersen GL, Anderson S, Appelbaum E, Arachchi HM, Armitage G, Arze CA, Ayvaz T, Baker CC, Begg L, Belachew T, Bhonagiri V, Bihan M, Blaser MJ, Bloom T, Bonazzi V, Brooks JP, Buck GA, Buhay CJ, Busam DA, Campbell JL, Canon SR, Cantarel BL, Chain PSG, Chen IMA, Chen L, Chhibba S, Chu K, Ciulla DM, Clemente JC, Clifton SW, Conlan S, Crabtree J, Cutting MA, Davidovics NJ, Davis CC, Desantis TZ, Deal C, Delehaunty KD, Dewhirst FE, Deych E, Ding Y, Dooling DJ, Dugan SP, Dunne WM, Durkin AS, Edgar RC, Erlich RL, Farmer CN, Farrell RM, Faust K, Feldgarden M, Felix VM, Fisher S, Fodor AA, Forney LJ, Foster L, di Francesco V, Friedman J, Friedrich DC, Fronick CC, Fulton LL, Gao HY, Garcia N, Giannoukos G, Giblin C, Giovanni MY, Goldberg JM, Goll J, Gonzalez A, Griggs A et al (2012) Structure, function and diversity of the healthy human microbiome. *Nature* 486:207–214
- Inan MS, Rasoulpour RJ, Yin L, Hubbard AK, Rosenberg DW, Giardina C (2000) The luminal short-chain fatty acid butyrate modulates NF-kappaB activity in a human colonic epithelial cell line. *Gastroenterology* 118:724–734
- Inoue K, Shirai T, Ochiai H, Kasao M, Hayakawa K, Kimura M, Sansawa H (2003) Blood-pressure-lowering effect of a novel fermented milk containing gamma-aminobutyric acid (GABA) in mild hypertensives. *Eur J Clin Nutr* 57:490–495
- Iwanaga T, Kishimoto A (2015) Cellular distributions of monocarboxylate transporters: a review. *Biomed Res* 36:279–301

- James SL, Christophersen CT, Bird AR, Conlon MA, Rosella O, Gibson PR, Muir JG (2015) Abnormal fibre usage in UC in remission. *Gut* 64:562–570
- Jenkins CLD, Lewis D, Bushell R, Belobrajdic DP, Bird AR (2011) Chain length of cereal fructans isolated from wheat stem and barley grain modulates in vitro fermentation. *J Cereal Sci* 53:188–191
- Jimenez E, Marin ML, Martin R, Odriozola JM, Olivares M, Xaus J, Fernandez L, Rodriguez JM (2008) Is meconium from healthy newborns actually sterile? *Res Microbiol* 159:187–193
- Keenan MJ, Zhou J, Hegsted M, Pelkman C, Durham HA, Coulon DB, Martin RJ (2015) Role of resistant starch in improving gut health, adiposity, and insulin resistance. *Adv Nutr* 6:198–205
- Khan KJ, Ullman TA, Ford AC, Abreu MT, Abadir A, Marshall JK, Talley NJ, Moayyedi P (2011) Antibiotic therapy in inflammatory bowel disease: a systematic review and meta-analysis. *Am J Gastroenterol* 106:661–673
- Kimberg DV, Field M, Johnson J, Henderson A, Gershon E (1971) Stimulation of intestinal mucosal adenylyl cyclase by cholera enterotoxin and prostaglandins. *J Clin Invest* 50:1218–1230
- Kleessen B, Hartmann L, Blaut M (2007a) Oligofructose and long-chain inulin: influence on the gut microbial ecology of rats associated with a human faecal flora. *Br J Nutr* 86:291
- Kleessen B, Schwarz S, Boehm A, Fuhrmann H, Richter A, Henle T, Krueger M (2007b) Jerusalem artichoke and chicory inulin in bakery products affect faecal microbiota of healthy volunteers. *Br J Nutr* 98:540–549
- Kleessen B, Stoof G, Proll J, Schmiel D, Noack J, Blaut M (1997) Feeding resistant starch affects fecal and cecal microflora and short-chain fatty acids in rats. *J Anim Sci* 75:2453–2462
- Koenig JE, Spor A, Scalfone N, Fricker AD, Stombaugh J, Knight R, Angenent LT, Ley RE (2011) Succession of microbial consortia in the developing infant gut microbiome. *Proc Natl Acad Sci USA* 108:4578–4585
- Komiyama Y, Andoh A, Fujiwara D, Ohmae H, Araki Y, Fujiyama Y, Mitsuyama K, Kanauchi O (2011) New prebiotics from rice bran ameliorate inflammation in murine colitis models through the modulation of intestinal homeostasis and the mucosal immune system. *Scand J Gastroenterol* 46:40–52
- Lanza E, Yu BB, Murphy G, Albert PS, Caan B, Marshall JR, Lance P, Paskett ED, Weissfeld J, Slattery M, Burt R, Iber F, Shike M, Kikendall JW, Brewer BK, Schatzkin A, Polyp Prevention Trial Study Group (2007) The polyp prevention trial-continued follow-up study: no effect of a low-fat, high-fiber, high-fruit, and—vegetable diet on adenoma recurrence eight years after randomization. *Cancer Epidemiol Biomark Prev* 16:1745–1752
- le Blay G, Michel C, Blottiere HM, Cherbut C (1999) Enhancement of butyrate production in the rat caecocolonic tract by long-term ingestion of resistant potato starch. *Br J Nutr* 82:419–426
- le Chatelier E, Nielsen T, Qin JJ, Prifti E, Hildebrand F, Falony G, Almeida M, Arumugam M, Batto JM, Kennedy S, Leonard P, Li JH, Burgdorf K, Garup N, Jorgensen T, Brandslund I, Nielsen HB, Juncker AS, Bertalan M, Levenez F, Pons N, Rasmussen S, Sunagawa S, Tap J, Tims S, Zoetendal EG, Brunak S, Clement K, Dore J, Kleerebezem M, Kristiansen K, Renault P, Sicheritz-Ponten T, de Vos WM, Zucker JD, Raes J, Hansen T, Bork P, Wang J, Ehrlich SD, Pedersen O, Meta HITC (2013) Richness of human gut microbiome correlates with metabolic markers. *Nature* 500:541
- le Leu R, Young G, Hu Y, Winter J, Conlon M (2013) Dietary red meat aggravates dextran sulfate sodium-induced colitis in mice whereas resistant starch attenuates inflammation. *Dig Dis Sci* 58:3475–3482
- le Leu RK, Winter JM, Christophersen CT, Young GP, Humphreys KJ, Hu Y, Gratz SW, Miller RB, Topping DL, Bird AR, Conlon MA (2015) Butyrylated starch intake can prevent red meat-induced O6-methyl-2-deoxyguanosine adducts in human rectal tissue: a randomised clinical trial. *Br J Nutr* 114:220–230
- le Poul E, Loison C, Struyf S, Springael JY, Lannoy V, Decobecq ME, Brezillon S, Dupriez V, Vassart G, van Damme J, Parmentier M, Detheux M (2003a) Functional characterization of human receptors for short chain fatty acids and their role in polymorphonuclear cell activation. *J Biol Chem* 278:25481–25489

- le Poul E, Loison C, Struyf S, Springael JY, Lannoy V, Decobecq ME, Brezillon S, Dupriez V, Vassart G, van Damme J, Parmentier M, Detheux M (2003b) Functional characterization of human receptors for short chain fatty acids and their role in polymorphonuclear cell activation. *J Biol Chem* 278:25481–25489
- Leach JD (2007) Evolutionary perspective on dietary intake of fibre and colorectal cancer. *Eur J Clin Nutr* 61:140–142
- Lecona E, Olmo N, Turnay J, Santiago-Gomez A, de Silanes IL, Gorospe M, Lizarbe MA (2008) Kinetic analysis of butyrate transport in human colon adenocarcinoma cells reveals two different carrier-mediated mechanisms. *Biochem J* 409:311–320
- Lee WJ, Hase K (2014) Gut microbiota-generated metabolites in animal health and disease. *Nat Chem Biol* 10:416–424
- Leitch EC, Walker AW, Duncan SH, Holtrop G, Flint HJ (2007a) Selective colonization of insoluble substrates by human faecal bacteria. *Environ Microbiol* 9:667–679
- Leitch ECM, Walker AW, Duncan SH, Holtrop G, Flint HJ (2007b) Selective colonization of insoluble substrates by human faecal bacteria. *Environ Microbiol* 9:667–679
- Lewis K, Lutgendorff F, Phan V, Soderholm JD, Sherman PM, McKay DM (2010) Enhanced translocation of bacteria across metabolically stressed epithelia is reduced by butyrate. *Inflamm Bowel Dis* 16:1138–1148
- Ley RE, Turnbaugh PJ, Klein S, Gordon JI (2006) Microbial ecology—human gut microbes associated with obesity. *Nature* 444:1022–1023
- Lin MY, de Zoete MR, Van Putten JP, Strijbis K (2015) Redirection of epithelial immune responses by short-chain fatty acids through inhibition of histone deacetylases. *Front Immunol* 6:554
- Louis P (2012) Does the human gut microbiota contribute to the etiology of autism spectrum disorders? *Dig Dis Sci* 57:1987–1989
- Luceri C, Femia AP, Fazi M, di Martino C, Zolfanelli F, Dolara P, Tonelli F (2016) Effect of butyrate enemas on gene expression profiles and endoscopic/histopathological scores of diverted colorectal mucosa: a randomized trial. *Dig Liver Dis* 48:27–33
- Lukito W, Malik SG, Surono IS, Wahlqvist ML (2015) From ‘lactose intolerance’ to ‘lactose nutrition’. *Asia Pac J Clin Nutr* 24:S1–S8
- Machiels K, Joossens M, Sabino J, De PV, Arijis I, Eeckhaut V, Ballet V, Claes K, Van IF, Verbeke K, Ferrante M, Verhaegen J, Rutgeerts P, Vermeire S (2013) A decrease of the butyrate-producing species *Roseburia hominis* and *Faecalibacterium prausnitzii* defines dysbiosis in patients with ulcerative colitis. *Gut* 63:1275–1283
- Machiels K, Joossens M, Sabino J, de Preter V, Arijis I, Eeckhaut V, Ballet V, Claes K, Van Immerseel F, Verbeke K, Ferrante M, Verhaegen J, Rutgeerts P, Vermeire S (2014) A decrease of the butyrate-producing species *Roseburia hominis* and *Faecalibacterium prausnitzii* defines dysbiosis in patients with ulcerative colitis. *Gut* 63:1275–1283
- Manichanh C, Rigottier-Gois L, Bonnaud E, Gloux K, Pelletier E, Frangeul L, Nalin R, Jarrin C, Chardon P, Marteau P, Roca J, Dore J (2006) Reduced diversity of faecal microbiota in Crohn’s disease revealed by a metagenomic approach. *Gut* 55:205–211
- Martin FPJ, Dumas ME, Wang YL, Legido-Quigley C, Yap IKS, Tang HR, Zirah S, Murphy GM, Cloarec O, Lindon JC, Sprenger N, Fay LB, Kochhar S, van Bladeren P, Holmes E, Nicholson JK (2007) A top-down systems biology view of microbiome-mammalian metabolic interactions in a mouse model. *Mol Syst Biol* 3:112
- Martin LJM, Dumon HJW, Champ MMJ (1998) Production of short-chain fatty acids from resistant starch in a pig model. *J Sci Food Agric* 77:71–80
- Martinez I, Kim J, Duffy PR, Schlegel VL, Walter J (2010) Resistant starches types 2 and 4 have differential effects on the composition of the fecal microbiota in human subjects. *PLoS One* 5: e15046
- Maslowski KM, Vieira AT, Ng A, Kranich J, Sierro F, Yu D, Schilter HC, Rolph MS, Mackay F, Artis D, Xavier RJ, Teixeira MM, Mackay CR (2009) Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43. *Nature* 461:1282–1286

- Mattila E, Uusitalo-Seppala R, Wuorela M, Lehtola L, Nurmi H, Ristikankare M, Moilanen V, Salminen K, Seppala M, Mattila PS, Anttila VJ, Arkkila P (2012) Fecal transplantation, through colonoscopy, is effective therapy for recurrent *Clostridium difficile* infection. *Gastroenterology* 142:490–496
- McOrist AL, Miller RB, Bird AR, Keogh JB, Noakes M, Topping DL, Conlon MA (2011) Fecal butyrate levels vary widely among individuals but are usually increased by a diet high in resistant starch. *J Nutr* 141:883–889
- Meddings JB, Jarand J, Urbanski SJ, Hardin J, Gall DG (1999) Increased gastrointestinal permeability is an early lesion in the spontaneously diabetic BB rat. *Am J Physiol* 276:G951–G957
- Michielan A, D’Inca R (2015) Intestinal permeability in inflammatory bowel disease: pathogenesis, clinical evaluation, and therapy of leaky gut. *Mediators Inflamm* 2015:628157
- Miller Jones J (2014) CODEX-aligned dietary fiber definitions help to bridge the ‘fiber gap’. *Nutr J* 13:34
- Muir JG, Rose R, Rosella O, Liels K, Barrett JS, Shepherd SJ, Gibson PR (2009) Measurement of short-chain carbohydrates in common Australian vegetables and fruits by high-performance liquid chromatography (HPLC). *J Agric Food Chem* 57:554–565
- Mulle JG, Sharp WG, Cubells JF (2013) The gut microbiome: a new frontier in autism research. *Curr Psychiatry Rep* 15:337
- Murphy N, Norat T, Ferrari P, Jenab M, Bueno-de-Mesquita B, Skeie G, Dahm CC, Overvad K, Olsen A, Tjønneland A, Clavel-Chapelon F, Boutron-Ruault MC, Racine A, Kaaks R, Teucher B, Boeing H, Bergmann MM, Trichopoulou A, Trichopoulos D, Lagiou P, Palli D, Pala V, Panico S, Tumino R, Vineis P, Siersema P, van Duijnhoven F, Peeters PHM, Hjartaker A, Engeset D, Gonzalez CA, Sanchez MJ, Dorronsoro M, Navarro C, Ardanaz E, Quiros JR, Sonestedt E, Ericson U, Nilsson L, Palmqvist R, Khaw KT, Wareham N, Key TJ, Crowe FL, Fedirko V, Wark PA, Chuang SC, Riboli E (2012) Dietary fibre intake and risks of cancers of the colon and rectum in the European Prospective Investigation into Cancer and Nutrition (EPIC). *PLoS One* 7:e39361
- Musch MW, Bookstein C, Xie Y, Sellin JH, Chang EB (2001) SCFA increase intestinal Na absorption by induction of NHE3 in rat colon and human intestinal C2/bbe cells. *Am J Physiol Gastrointest Liver Physiol* 280:G687–G693
- Naseer MI, Bibi F, Alqahtani MH, Chaudhary AG, Azhar EI, Kamal MA, Yasir M (2014) Role of gut microbiota in obesity, type 2 diabetes and Alzheimer’s disease. *CNS Neurol Disord-Drug Targets* 13:305–311
- Nemani K, Ghomi RH, McCormick B, Fan XD (2015) Schizophrenia and the gut-brain axis. *Prog Neuropsychopharmacol Biol Psychiatry* 56:155–160
- Nicholson JK, Holmes E, Kinross J, Burcelin R, Gibson G, Jia W, Pettersson S (2012) Host-gut microbiota metabolic interactions. *Science* 336:1262–1267
- Nicholson JK, Holmes E, Wilson ID (2005) Gut microorganisms, mammalian metabolism and personalized health care. *Nat Rev Microbiol* 3:431–438
- Norat T, Bingham S, Ferrari P, Slimani N, Jenab M, Mazuir M, Overvad K, Olsen A, Tjønneland A, Clavel F, Boutron-Ruault MC, Kesse E, Boeing H, Bergmann MM, Nieters A, Linseisen J, Trichopoulou A, Trichopoulos D, Tountas Y, Berrino F, Palli D, Panico S, Tumino R, Vineis P, Bueno-de-Mesquita HB, Peeters PHM, Engeset D, Lund E, Skeie G, Ardanaz E, Gonzalez C, Navarro C, Quiros JR, Sanchez MJ, Berglund G, Mattisson I, Hallmans G, Palmqvist R, Day NE, Khaw KT, Key TJ, San Joaquin M, Hemon B, Saracci R, Kaaks R, Riboli E (2005) Meat, fish, and colorectal cancer risk: the European prospective investigation into cancer and nutrition. *J Natl Cancer Inst* 97:906–916
- O’Callaghan NJ, Toden S, Bird AR, Topping DL, Fenech M, Conlon MA (2012) Colonocyte telomere shortening is greater with dietary red meat than white meat and is attenuated by resistant starch. *Clin Nutr* 31:60–64
- O’Keefe SJD, Chung D, Mahmoud N, Sepulveda AR, Manafe M, Arch J, Adada H, van der Merwe T (2007) Why do African Americans get more colon cancer than native Africans? *J Nutr* 137:175S–182S

- Ou JH, Delany JP, Zhang M, Sharma S, O'Keefe SJD (2012) Association between low colonic short-chain fatty acids and high bile acids in high colon cancer risk populations. *Nutr Cancer Int J* 64:34–40
- Pal S, Murugan C, Clarke JM, Young GP, Ramakrishna BS, Lockett T (2013) Esterified starch as a treatment for acute gastroenteritis—a double blind randomized controlled trial. *Gastroenterology* 144:S904
- Park Y, Hunter DJ, Spiegelman D, Bergkvist L, Berrino F, Van den Brandt PA, Buring JE, Colditz GA, Freudenheim JL, Fuchs CS, Giovannucci E, Goldbohm RA, Graham S, Harnack L, Hartman AM, Jacobs DR, Kato I, Krogh V, Leitzmann MF, McCullough ML, Miller AB, Pietinen P, Rohan TE, Schatzkin A, Willett WC, Wolk A, Zeleniuch-Jacquotte A, Zhang SMM, Smith-Warner SA (2005) Dietary fiber intake and risk of colorectal cancer—a pooled analysis of prospective cohort studies. *Jama-J Am Med Assoc* 294:2849–2857
- Parsons BN, Wigley P, Simpson HL, Williams JM, Humphrey S, Salisbury AM, Watson AJ, Fry SC, O'Brien D, Roberts CL, O'Kennedy N, Keita AV, Soderholm JD, Rhodes JM, Campbell BJ (2014) Dietary supplementation with soluble plantain non-starch polysaccharides inhibits intestinal invasion of *Salmonella Typhimurium* in the chicken. *PLoS One* 9:e87658
- Peeters M, Geypens B, Claus D, Nevens H, Ghooys Y, Verbeke G, Baert F, Vermeire S, Vlietinck R, Rutgeerts P (1997) Clustering of increased small intestinal permeability in families with Crohn's disease. *Gastroenterology* 113:802–807
- Perrier C, Corthesy B (2011) Gut permeability and food allergies. *Clin Exp Allergy* 41:20–28
- Piche T (2014) Tight junctions and IBS—the link between epithelial permeability, low-grade inflammation, and symptom generation? *Neurogastroenterol Motil* 26:296–302
- Ploger S, Stumpff F, Penner GB, Schulzke JD, Gabel G, Martens H, Shen Z, Gunzel D, Aschenbach JR (2012) Microbial butyrate and its role for barrier function in the gastrointestinal tract. *Ann NY Acad Sci* 1258:52–59
- Png CW, Linden SK, Gilshenan KS, Zoetendal EG, McSweeney CS, Sly LI, McGuckin MA, Florin THJ (2010) Mucolytic bacteria with increased prevalence in IBD mucosa augment in vitro utilization of mucin by other bacteria. *Am J Gastroenterol* 105:2420–2428
- Puddu A, Sanguineti R, Montecucco F, Viviani GL (2014) Evidence for the gut microbiota short-chain fatty acids as key pathophysiological molecules improving diabetes. *Mediators Inflamm* 2014:162021
- Pullan RD, Thomas GA, Rhodes M, Newcombe RG, Williams GT, Allen A, Rhodes J (1994) Thickness of adherent mucus gel on colonic mucosa in humans and its relevance to colitis. *Gut* 35:353–359
- Qin JJ, Li RQ, Raes J, Arumugam M, Burgdorf KS, Manichanh C, Nielsen T, Pons N, Levenez F, Yamada T, Mende DR, Li JH, Xu JM, Li SC, Li DF, Cao JJ, Wang B, Liang HQ, Zheng HS, Xie YL, Tap J, Lepage P, Bertalan M, Batto JM, Hansen T, le Paslier D, Linneberg A, Nielsen HB, Pelletier E, Renault P, Sicheritz-Ponten T, Turner K, Zhu HM, Yu C, Li ST, Jian M, Zhou Y, Li YR, Zhang XQ, Li SG, Qin N, Yang HM, Wang J, Brunak S, Dore J, Guarner F, Kristiansen K, Pedersen O, Parkhill J, Weissenbach J, Bork P, Ehrlich SD, Wang J, Meta HITC (2010) A human gut microbial gene catalogue established by metagenomic sequencing. *Nature* 464:59–65
- Qin JJ, Li YR, Cai ZM, Li SH, Zhu JF, Zhang F, Liang SS, Zhang WW, Guan YL, Shen DQ, Peng YQ, Zhang DY, Jie ZY, Wu WX, Qin YW, Xue WB, Li JH, Han LC, Lu DH, Wu PX, Dai YL, Sun XJ, Li ZS, Tang AF, Zhong SL, Li XP, Chen WN, Xu R, Wang MB, Feng Q, Gong MH, Yu J, Zhang YY, Zhang M, Hansen T, Sanchez G, Raes J, Falony G, Okuda S, Almeida M, Lechatelier E, Renault P, Pons N, Batto JM, Zhang ZX, Chen H, Yang RF, Zheng WM, Li SG, Yang HM, Wang J, Ehrlich SD, Nielsen R, Pedersen O, Kristiansen K, Wang J (2012) A metagenome-wide association study of gut microbiota in type 2 diabetes. *Nature* 490:55–60
- Raghupathy P, Ramakrishna BS, Oommen SP, Ahmed TS, Priyaa T, Dziura J, Young GP, Binder HJ (2006) Amylase-resistant starch as adjunct to oral rehydration therapy in children with diarrhea. *J Pediatr Gastroenterol Nutr* 42:362–368

- Rajendran VM, Binder HJ (1994) Apical membrane Cl-butyrate exchange: mechanism of short chain fatty acid stimulation of active chloride absorption in rat distal colon. *J Membr Biol* 141:51–58
- Rajilic-Stojanovic M, Shanahan F, Guarner F, de Vos WM (2013) Phylogenetic analysis of dysbiosis in ulcerative colitis during remission. *Inflamm Bowel Dis* 19:481–488
- Ramakrishna BS, Nance SH, Roberts-Thomson IC, Roediger WE (1990) The effects of enterotoxins and short-chain fatty acids on water and electrolyte fluxes in ileal and colonic loops in vivo in the rat. *Digestion* 45:93–101
- Ramakrishna BS, Venkataraman S, Srinivasan P, Dash P, Young GP, Binder HJ (2000) Amylase-resistant starch plus oral rehydration solution for cholera. *N Engl J Med* 342:308–313
- Ramirez-Farias C, Slezak K, Fuller Z, Duncan A, Holtrop G, Louis P (2009) Effect of inulin on the human gut microbiota: stimulation of *Bifidobacterium adolescentis* and *Faecalibacterium prausnitzii*. *Br J Nutr* 101:541–550
- Ridaura VK, Faith JJ, Rey FE, Cheng JY, Duncan AE, Kau AL, Griffin NW, Lombard V, Henrissat B, Bain JR, Muehlbauer MJ, Ilkayeva O, Semenkovich CF, Funai K, Hayashi DK, Lyle BJ, Martini MC, Ursell LK, Clemente JC, Van Treuren W, Walters WA, Knight R, Newgard CB, Heath AC, Gordon JI (2013) Gut microbiota from twins discordant for obesity modulate metabolism in mice. *Science* 341:1079
- Roberfroid MB (2005) Introducing inulin-type fructans. *Br J Nutr* 93:S13–S25
- Roberfroid MB (2007) Inulin-type fructans: functional food ingredients. *J Nutr* 137:2493S–2502S
- Roberts CL, Keita AV, Duncan SH, O’Kennedy N, Soderholm JD, Rhodes JM, Campbell BJ (2010) Translocation of Crohn’s disease *Escherichia coli* across M-cells: contrasting effects of soluble plant fibres and emulsifiers. *Gut* 59:1331–1339
- Roberts CL, Keita AV, Parsons BN, Prorok-Hamon M, Knight P, Winstanley C, O’Kennedy N, Soderholm JD, Rhodes JM, Campbell BJ (2013) Soluble plantain fibre blocks adhesion and M-cell translocation of intestinal pathogens. *J Nutr Biochem* 24:97–103
- Said HM (2011) Intestinal absorption of water-soluble vitamins in health and disease. *Biochem J* 437:357–372
- Sakaguchi S, Yamaguchi T, Nomura T, Ono M (2008) Regulatory T cells and immune tolerance. *Cell* 133:775–787
- Savage DC (1977) Microbial ecology of gastrointestinal-tract. *Annu Rev Microbiol* 31:107–133
- Schamberger GP, Diez-Gonzalez F (2002) Selection of recently isolated colicinogenic *Escherichia coli* strains inhibitory to *Escherichia coli* O157: H7. *J Food Prot* 65:1381–1387
- Scheperjans F, Aho V, Pereira PAB, Koskinen K, Paulin L, Pekkonen E, Haapaniemi E, Kaakkola S, Eerola-Rautio J, Pohja M, Kinnunen E, Murros K, Auvinen P (2015) Gut microbiota are related to Parkinson’s disease and clinical phenotype. *Mov Disord* 30:350–358
- Scheppach W (1996) Treatment of distal ulcerative colitis with short-chain fatty acid enemas. a placebo-controlled trial. German-Austrian SCFA Study Group. *Dig Dis Sci* 41:2254–2259
- Schieber AM, Lee YM, Chang MW, Leblanc M, Collins B, Downes M, Evans RM, Ayres JS (2015) Disease tolerance mediated by microbiome *E. coli* involves inflammasome and IGF-1 signaling. *Science* 350:558–563
- Schneeman BO (1986) Dietary fiber—physical and chemical-properties, methods of analysis, and physiological-effects. *Food Technol* 40:104–110
- Segal I, Edwards CA, Walker ARP (2000) Continuing low colon cancer incidence in African populations. *Am J Gastroenterol* 95:859–860
- Sellon RK, Tonkonogy S, Schultz M, Dieleman LA, Grenther W, Balish E, Rennick DM, Sartor RB (1998) Resident enteric bacteria are necessary for development of spontaneous colitis and immune system activation in interleukin-10-deficient mice. *Infect Immun* 66:5224–5231
- Singh N, Gurav A, Sivaprakasam S, Brady E, Padia R, Shi H, Thangaraju M, Prasad PD, Manicassamy S, Munn DH, Lee JR, Offermanns S, Ganapathy V (2014) Activation of Gpr109a, receptor for niacin and the commensal metabolite butyrate, suppresses colonic inflammation and carcinogenesis. *Immunity* 40:128–139
- Slavin JL (2001) Dietary fiber and colon cancer. Marcel Dekker Inc, New York

- Smith K, McCoy KD, Macpherson AJ (2007) Use of axenic animals in studying the adaptation of mammals to their commensal intestinal microbiota. *Semin Immunol* 19:59–69
- Smith PM, Howitt MR, Panikov N, Michaud M, Gallini CA, Bohlooly Y, Glickman JN, Garrett WS (2013) The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. *Science* 341:569–573
- Sokol H, Pigneur B, Watterlot L, Lakhdari O, Bermudez-Humaran LG, Gratadoux JJ, Blugeon S, Bridonneau C, Furet JP, Corthier G, Grange C, Vasquez N, Pochart P, Trugnan G, Thomas G, Blottiere HM, Dore J, Marteau P, Seksik P, Langella P (2008) *Faecalibacterium prausnitzii* is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. *Proc Natl Acad Sci USA* 105:16731–16736
- Soliman ML, Rosenberger TA (2011) Acetate supplementation increases brain histone acetylation and inhibits histone deacetylase activity and expression. *Mol Cell Biochem* 352:173–180
- Steinhart AH, Hiruki T, Brzezinski A, Baker JP (1996) Treatment of left-sided ulcerative colitis with butyrate enemas: a controlled trial. *Aliment Pharmacol Ther* 10:729–736
- Stephen AM (1994) Whole grains—impact of consuming whole grains on physiological-effects of dietary fiber and starch. *Crit Rev Food Sci Nutr* 34:499–511
- Subramanya S, Ramakrishna BS, Binder HJ, Farthing MJ, Young GP (2006) Evaluation of oral rehydration solution by whole-gut perfusion in rats: effect of osmolarity, sodium concentration and resistant starch. *J Pediatr Gastroenterol Nutr* 43:568–575
- Subramanya SB, Rajendran VM, Srinivasan P, Kumar NSN, Ramakrishna BS, Binder HJ (2007) Differential regulation of cholera toxin-inhibited Na-H exchange isoforms by butyrate in rat ileum. *Am J Physiol Gastrointest. Liver Physiol* 293:G857–G863
- Suzuki T, Yoshida S, Hara H (2008) Physiological concentrations of short-chain fatty acids immediately suppress colonic epithelial permeability. *Br J Nutr* 100:297–305
- Swidsinski A, Loening-Boecker V, Herber A (2009) Mucosal flora in Crohn's disease and ulcerative colitis—an overview. *J Physiol Pharmacol* 60(suppl 6):61–71
- Takahashi K, Nishida A, Fujimoto T, Fujii M, Shioya M, Imaeda H, Inatomi O, Bamba S, Andoh A, Sugimoto M (2016) Reduced abundance of butyrate-producing bacteria species in the fecal microbial community in Crohn's disease. *Digestion* 93:59–65
- Tan J, McKenzie C, Potamitis M, Thorburn AN, Mackay CR, Macia L (2014) The role of short-chain fatty acids in health and disease. *Adv Immunol* 121:91–119
- Tao R, de Zoeten EF, Ozkaynak E, Chen C, Wang L, Porrett PM, Li B, Turka LA, Olson EN, Greene MI, Wells AD, Hancock WW (2007) Deacetylase inhibition promotes the generation and function of regulatory T cells. *Nat Med* 13:1299–1307
- Tennant DR (2014) Potential intakes of total polyols based on UK usage survey data. *Food Addit Contam Part A-Chem Anal Control Exposure Risk Assess* 31:574–586
- Thangaraju M, Cresci GA, Liu K, Ananth S, Gnanaprakasam JP, Browning DD, Mellinger JD, Smith SB, Digby GJ, Lambert NA, Prasad PD, Ganapathy V (2009) GPR109A is a G-protein-coupled receptor for the bacterial fermentation product butyrate and functions as a tumor suppressor in colon. *Cancer Res* 69:2826–2832
- Thibault R, Blachier F, Darcy-Vrillon B, De CP, Bourreille A, Segain JP (2010) Butyrate utilization by the colonic mucosa in inflammatory bowel diseases: a transport deficiency. *Inflamm Bowel Dis* 16:684–695
- Thibault R, de Coppet P, Daly K, Bourreille A, Cuff M, Bonnet C, Mosnier JF, Galmiche JP, Shirazi-Beechey S, Segain JP (2007) Down-regulation of the monocarboxylate transporter 1 is involved in butyrate deficiency during intestinal inflammation. *Gastroenterology* 133:1916–1927
- Thorburn AN, McKenzie CI, Shen S, Stanley D, Macia L, Mason LJ, Roberts LK, Wong CH, Shim R, Robert R, Chevalier N, Tan JK, Marino E, Moore RJ, Wong L, McConville MJ, Tull DL, Wood LG, Murphy VE, Mattes J, Gibson PG, Mackay CR (2015) Evidence that asthma is a developmental origin disease influenced by maternal diet and bacterial metabolites. *Nat Commun* 6:7320
- Thornton JR, Dryden A, Kelleher J, Losowsky MS (1987) Super-efficient starch absorption—a risk factor for colonic neoplasia. *Dig Dis Sci* 32:1088–1091

- Toden S, Bird AR, Topping DL, Conlon MA (2007) High red meat diets induce greater numbers of colonic DNA double-strand breaks than white meat in rats: attenuation by high-amylose maize starch. *Carcinogenesis* 28:2355–2362
- Toden S, Lockett TJ, Topping DL, Scherer BL, Watson EJ, Southwood JG, Clarke JM (2014) Butyrylated starch affects colorectal cancer markers beneficially and dose-dependently in genotoxin-treated rats. *Cancer Biol Ther* 15:1515–1523
- Tolhurst G, Heffron H, Lam YS, Parker HE, Habib AM, Diakogiannaki E, Cameron J, Grosse J, Reimann F, Gribble FM (2012) Short-chain fatty acids stimulate glucagon-like peptide-1 secretion via the G-protein-coupled receptor FFAR2. *Diabetes* 61:364–371
- Topping D (2007) Cereal complex carbohydrates and their contribution to human health. *J Cereal Sci* 46:220–229
- Topping DL, Bird AR (1999) Foods, nutrients and digestive health. *Aust J Nutr Diet* 56:S22–S34
- Topping DL, Clifton PM (2001) Short-chain fatty acids and human colonic function: roles of resistant starch and nonstarch polysaccharides. *Physiol Rev* 81:1031–1064
- Topping DL, Illman RJ (1986) Bacterial fermentation in the human large-bowel—time to change from the roughage model of dietary fiber. *Med J Austral* 144:307–309
- Tosh SM, Brummer Y, Wolever TMS, Wood PJ (2008) Glycemic response to oat bran muffins treated to vary molecular weight of beta-glucan. *Cereal Chem* 85:211–217
- Trowell HC, Burkitt DP (1987) The development of the concept of dietary fiber. *Mol Aspects Med* 9:7–15
- Tungland BC, Meyer D (2002) Nondigestible oligo—and polysaccharides (Dietary fiber): their physiology and role in human health and food. *Compr Rev Food Sci Food Saf* 1:73–92
- Tuohy KM, Conterno L, Gasperotti M, Viola R (2012) Up-regulating the human intestinal microbiome using whole plant foods, polyphenols, and/or fiber. *J Agric Food Chem* 60:8776–8782
- Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI (2006) An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* 444:1027–1031
- Vadivel G, Prasad PD, Thangaraju M, Martin PM, Singh N (2014) Butyrate-mediated protection against colonic inflammation and colon carcinogenesis: role of butyrate transporters and butyrate receptors. Food sources, functions and health benefits, Butyrate
- Van den Abbeele P, Gerard P, Rabot S, Bruneau A, El Aidy S, Derrien M, Kleerebezem M, Zoetendal EG, Smidt H, Verstraete W, Van de Wiele T, Possemiers S (2011) Arabinoxylans and inulin differentially modulate the mucosal and luminal gut microbiota and mucin-degradation in humanized rats. *Environ Microbiol* 13:2667–2680
- Van der Merwe B, Erasmus C, Taylor JRN (2001) African maize porridge: a food with slow in vitro starch digestibility. *Food Chem* 72:347–353
- Vieira ELM, Leonel AJ, Sad AP, Beltrao NRM, Costa TF, Ferreira TMR, Gomes-Santos AC, Faria AMC, Peluzio MCG, Cara DC, Alvarez-Leite JI (2012) Oral administration of sodium butyrate attenuates inflammation and mucosal lesion in experimental acute ulcerative colitis. *J Nutr Biochem* 23:430–436
- Vinolo MA, Rodrigues HG, Hatanaka E, Hebeda CB, Farsky SH, Curi R (2009) Short-chain fatty acids stimulate the migration of neutrophils to inflammatory sites. *Clin Sci (Lond)* 117:331–338
- Vinolo MA, Rodrigues HG, Hatanaka E, Sato FT, Sampaio SC, Curi R (2011a) Suppressive effect of short-chain fatty acids on production of proinflammatory mediators by neutrophils. *J Nutr Biochem* 22:849–855
- Vinolo MA, Rodrigues HG, Nachbar RT, Curi R (2011b) Regulation of inflammation by short chain fatty acids. *Nutrients* 3:858–876
- Vivinus-Nebot M, Frin-Mathy G, Bziouche H, Dainese R, Bernard G, Anty R, Filippi J, Saint-Paul MC, Tulic MK, Verhasselt V, Hebuerne X, Piche T (2014) Functional bowel symptoms in quiescent inflammatory bowel diseases: role of epithelial barrier disruption and low-grade inflammation. *Gut* 63:744–752
- Wahlqvist ML (2015) Lactose nutrition in lactase nonpersisters. *Asia Pac J Clin Nutr* 24:S21–S25

- Walker ARP, Walker BF, Walker AJ (1986) Fecal pH, dietary fiber intake, and proneness to colon cancer in 4 South-African populations. *Br J Cancer* 53:489–495
- Walker AW, Ince J, Duncan SH, Webster LM, Holtrop G, Ze X, Brown D, Stares MD, Scott P, Bergerat A, Louis P, McIntosh F, Johnstone AM, Lobley GE, Parkhill J, Flint HJ (2011) Dominant and diet-responsive groups of bacteria within the human colonic microbiota. *ISME J* 5:220–230
- Wang HB, Wang PY, Wang X, Wan YL, Liu YC (2012) Butyrate enhances intestinal epithelial barrier function via up-regulation of tight junction protein Claudin-1 transcription. *Dig Dis Sci* 57:3126–3135
- Wang L, Christophersen CT, Sorich MJ, Gerber JP, Angley MT, Conlon MA (2011) Low relative abundances of the mucolytic bacterium *Akkermansia muciniphila* and *Bifidobacterium* spp. in feces of children with autism. *Appl Environ Microbiol* 77:6718–6721
- West NP, Christophersen CT, Pyne DB, Cripps AW, Conlon MA, Topping DL, Kang S, McSweeney CS, Fricker PA, Aguirre D, Clarke JM (2013) Butyrylated starch increases colonic butyrate concentration but has limited effects on immunity in healthy physically active individuals. *Exerc Immunol Rev* 19:102–119
- Windey K, de Preter V, Verbeke K (2012) Relevance of protein fermentation to gut health. *Mol Nutr Food Res* 56:184–196
- Windey K, Houben E, Deroover L, Verbeke K (2015) Contribution of colonic fermentation and fecal water toxicity to the pathophysiology of lactose-intolerance. *Nutrients* 7:7505–7522
- Winter J, Nyskohus L, Young GP, Hu Y, Conlon MA, Bird AR, Topping DL, Le Leu RK (2011) Inhibition by resistant starch of red meat-induced promutagenic adducts in mouse colon. *Cancer Prev Res* 4:1920–1928
- Wong JMW, de Souza R, Kendall CWC, Emam A, Jenkins DJA (2006) Colonic health: fermentation and short chain fatty acids. *J Clin Gastroenterol* 40:235–243
- Xu H, McCoy A, Li J, Zhao Y, Ghishan FK (2015) Sodium butyrate stimulates NHE8 expression via its role on activating NHE8 basal promoter activity. *Am Physiol-Gastrointest Liver Physiol* 309:G500–G505
- Yatsunenko T, Rey FE, Manary MJ, Trehan I, Dominguez-Bello MG, Contreras M, Magris M, Hidalgo G, Baldassano RN, Anokhin AP, Heath AC, Warner B, Reeder J, Kuczynski J, Caporaso JG, Lozupone CA, Lauber C, Clemente JC, Knights D, Knight R, Gordon JI (2012) Human gut microbiome viewed across age and geography. *Nature* 486:222
- Yetukuri L, Ekroos K, Vidal-Puig A, Oresic M (2008) Informatics and computational strategies for the study of lipids. *Mol Biosyst* 4:121–127
- Yu YN, Fang JY (2015) Gut microbiota and colorectal cancer. *Gastrointest Tumors* 2:26–32
- Ze X, Duncan SH, Louis P, Flint HJ (2012) *Ruminococcus bromii* is a keystone species for the degradation of resistant starch in the human colon. *ISME J* 6:1535–1543
- Zeissig S, Burgel N, Gunzel D, Richter J, Mankertz J, Wahnschaffe U, Kroesen AJ, Zeitz M, Fromm M, Schulzke JD (2007) Changes in expression and distribution of claudin 2, 5 and 8 lead to discontinuous tight junctions and barrier dysfunction in active Crohn's disease. *Gut* 56:61–72

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